The American Journal of Medicine

The American Journal of Medicine

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CONTENTS

The American Journal of Medicine

Vol. XXI JULY, 1956 No. 1

Editorial

Clinical Studies

This is a provocative paper on an important but highly controversial subject, namely, the nature of the probable heterogeneous forms of hepatic cirrhosis encountered with disquieting frequency in relatively young women who give no history of overt acute hepatitis. The authors summarize their experience in twenty-six such cases, some cited in illustrative detail. It is made clear that the age and sex incidence, the prevalence of arthritis, the obscure febrile episodes and other manifestations are unusual for classic Laennec's cirrhosis and raise the question whether, in some instances at least, these cases may constitute distinct forms of cirrhosis.

The authors attempt to evaluate the role, recently challenged, of portal hypertension *per se* in the pathogenesis of ascites. They find that ascites occurred in five of fifteen patients with marked portal hypertension due solely to chronic occlusion of the extrahepatic portion of the portal vein, notably in those instances in which by-passing "hepatopetal," collateral portal vein circulation was not well developed. This indicates that ascites may appear as a result of hypertension in the extrahepatic portal system alone, with no apparent increase in hydrostatic pressure within the intrahepatic portal or hepatic venous system. However, the results would also seem to imply that extrahepatic portal vein hypertension is not as critical a factor in ascites formation as formerly was assumed.

While the prevalence of liver involvement in infectious mononucleosis is now generally recognized, many points in this connection remain controversial. Among other things brought out in this study is the occasional absence of significant heterophil antibody production in patients who show typical clinical manifestations of infectious mononucleosis, with consistent liver biopsy findings, and the (even rarer) occurrence of persistent structural changes indicative of chronic hepatitis.

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does more for asthmatics

more rapid relief · more certain control · greater safety

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VOLUME TWENTY-ONE NUMBER ONE

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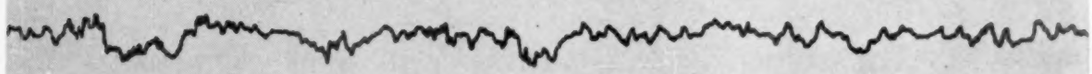
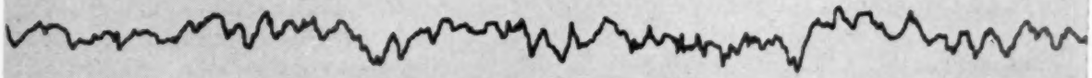
WHAT IS THE DIFFERENCE BETWEEN A TRANQUILIZER AND A SEDATIVE?

Comparison of the effect of Raudixin (tranquilizer) and a barbiturate (sedative) on the cortical electroencephalogram



No drug.



After Raudixin. E. E. G. not altered.

After barbiturate. Typical "spindling" effect.

Because barbiturates and other sedatives depress the cerebral cortex, the sedation achieved is accompanied by a reduction in mental alertness.

Raudixin acts in the area of the midbrain and diencephalon, and does not depress the cerebral cortex. Consequently, the tranquilizing (ataractic) effect achieved is generally free of loss of alertness.

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SUPPLY: 50 mg. and 100 mg. tablets; bottles of 100, 1000 and 5000.

SQUIBB

Squibb Quality—the Priceless Ingredient

CONTENTS continued—July 1956

VOLUME TWENTY-ONE NUMBER ONE

Review

Dr. Hartman attempts to survey and classify the allergic disorders—considered in their broadest sense. The classification is of necessity arbitrary and open to disputation on many points. Nevertheless it serves to remind us forcefully of the importance and diversity of abnormal immune mechanisms in disease and also of the overlapping interests which threaten to displace the specialist in allergy altogether from these various disciplines which the author seeks to confine. We have here the all too common conflict between the practical necessity for compartmentalization of special skills and the equally valid philosophical necessity for the comprehensive approach to disease.

Seminar on Diseases of the Pancreas

This paper appropriately introduces the Seminar on Pancreatic Diseases by summarizing present knowledge of the exocrine pancreatic secretion in the normal human subject and in patients with disease of the pancreas. The authors first consider the composition of the pancreatic juice, the anatomic and physiologic factors, which affect pancreatic secretion in the normal subject, and the nature of the pancreatic enzymes. The discussion then goes on to abnormalities of the exocrine pancreatic secretion as encountered in various disease states and the clinical implications thereof. There is a notable section on the use of the secretin test.

Clinico-pathologic Conference

Clinico-pathologic conference (Washington University School of Medicine)

Research Society Abstracts

Case Reports

The syndrome which has been and is here designated chronic idiopathic jaundice belongs in the general family of what is commonly called constitutional hyperbilirubinemia. This disorder, easily confused with other causes of chronic and recurrent jaundice, may well be a manifestation of some obscure inborn or acquired error in bile pigment metabolism. The two cases cited in this interesting report are well worth study.

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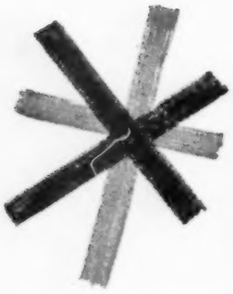

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ROSE FEVER

Supplied in 5-cc vials, each cc containing 40 U.S.P. units of corticotropin adsorbed on zinc hydroxide (2.0 mg zinc/cc)

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†*Patent Pending. Available in other countries as Cortrophine-Z.*

†*Organon brand of Corticotropin-Zinc Hydroxide*

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CONTENTS continued–July 1956

VOLUME TWENTY-ONE NUMBER ONE

Advertising Index on 3rd Cover

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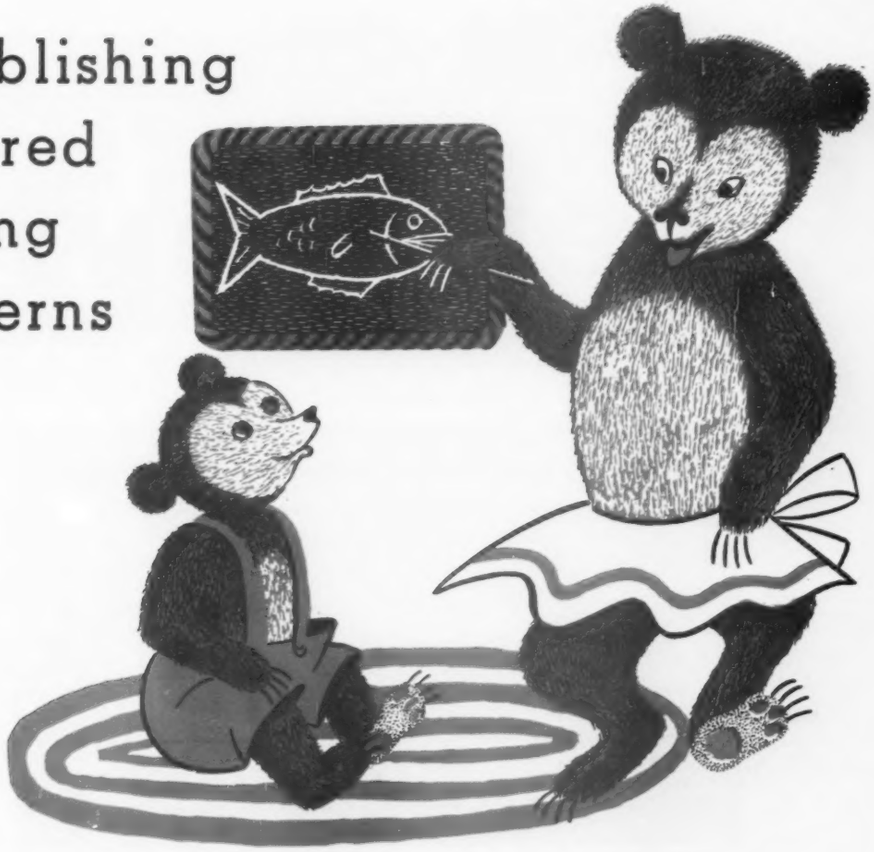
establishing desired eating patterns



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Formula

Semoxydrine HCl (Methamphetamine HCl) 5 mg.; Pentobarbital 20 mg.; Ascorbic acid 100 mg.; Thiamine HCl 0.5 mg.; Riboflavin 1 mg.; Niacin 5 mg.

1. Eisfelder, H.W.: Am. Pract. & Dig. Treat., 5:778 (Oct.) 1954).
2. Sebrell, W.H., Jr.: J.A.M.A., 152:42 (May, 1953).
3. Sherman, R.J.: Medical Times, 82:107 (Feb., 1954).

Write for 60-10-70 Menu pads, weight charts, and samples of Obedrin.

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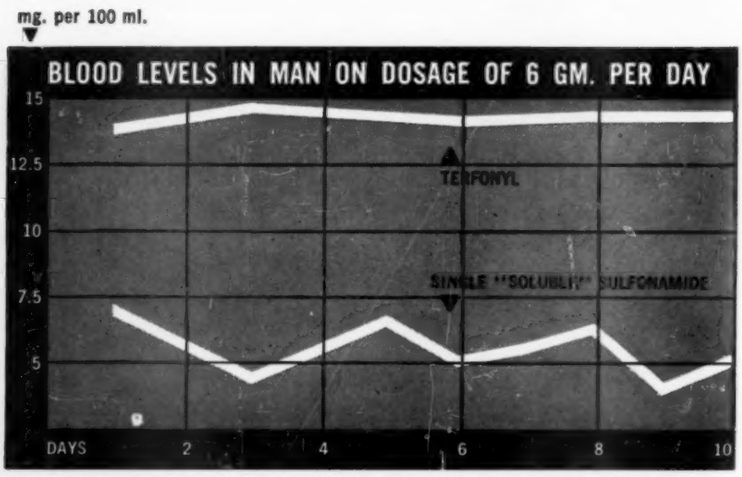
BRISTOL, TENNESSEE

maximum efficacy with minimum risk

Terfonyl

SQUIBB METH-DIA-MER SULFONAMIDES



— After Lehr, D., Modern Med. 23:111 (Jan. 15) 1955.

Terfonyl is absorbed as well as single "soluble" sulfonamides, but is eliminated at a slower rate. For this reason, Terfonyl blood levels are much higher.

In experimental infections (Klebsiella, Pneumococcus, Streptococcus), Meth-Dia-Mer sulfonamides have been shown to be from three to four times more effective on a weight basis than single "soluble" sulfonamides.

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0.167 Gm. each of sulfamethazine, sulfadiazine and sulfamerazine per tablet or per 5 ml. teaspoonful of suspension.

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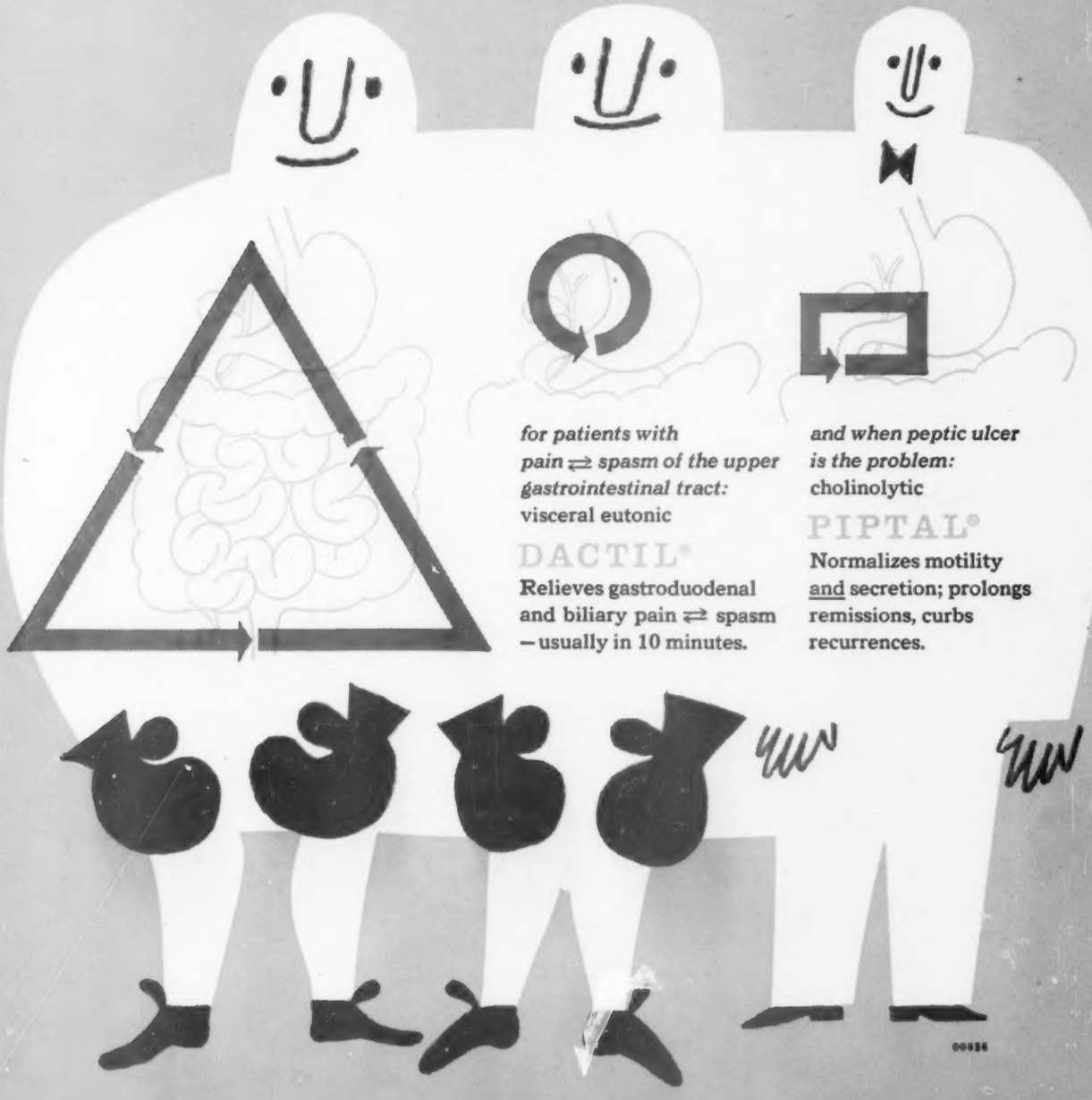
favorite for generalized G.I. dysfunction

TRIDAL

paired piperidol action

gives rapid, prolonged relief throughout the G.I. tract



for patients with pain ⇄ spasm of the upper gastrointestinal tract:
visceral eutonic

DACTIL®

Relieves gastroduodenal and biliary pain ⇄ spasm —usually in 10 minutes.

and when peptic ulcer is the problem:
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Normalizes motility and secretion; prolongs remissions, curbs recurrences.

Patients on TRIDAL, DACTIL or PIPTAL remain singularly free of anticholinergic-antispasmodic side effects.

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Full Diuretic Control with Fewer Injections

The THIOMERIN program combines parenteral and suppository therapy to solve a major diuretic problem—drastic diuresis, patient alternately dry and waterlogged.

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Supplied: THIOMERIN Suppositories, boxes of 12. Injection THIOMERIN Solution, vials of 2 cc., boxes of 12; vials of 10 cc. Injection THIOMERIN (lyophilized), vials of 1.4 Gm. (10 cc. upon reconstitution) and 4.2 Gm. (30 cc. upon reconstitution).

1. Daly, J.W.: Am. J. M. Sc. *228*:440 (Oct.) 1954.

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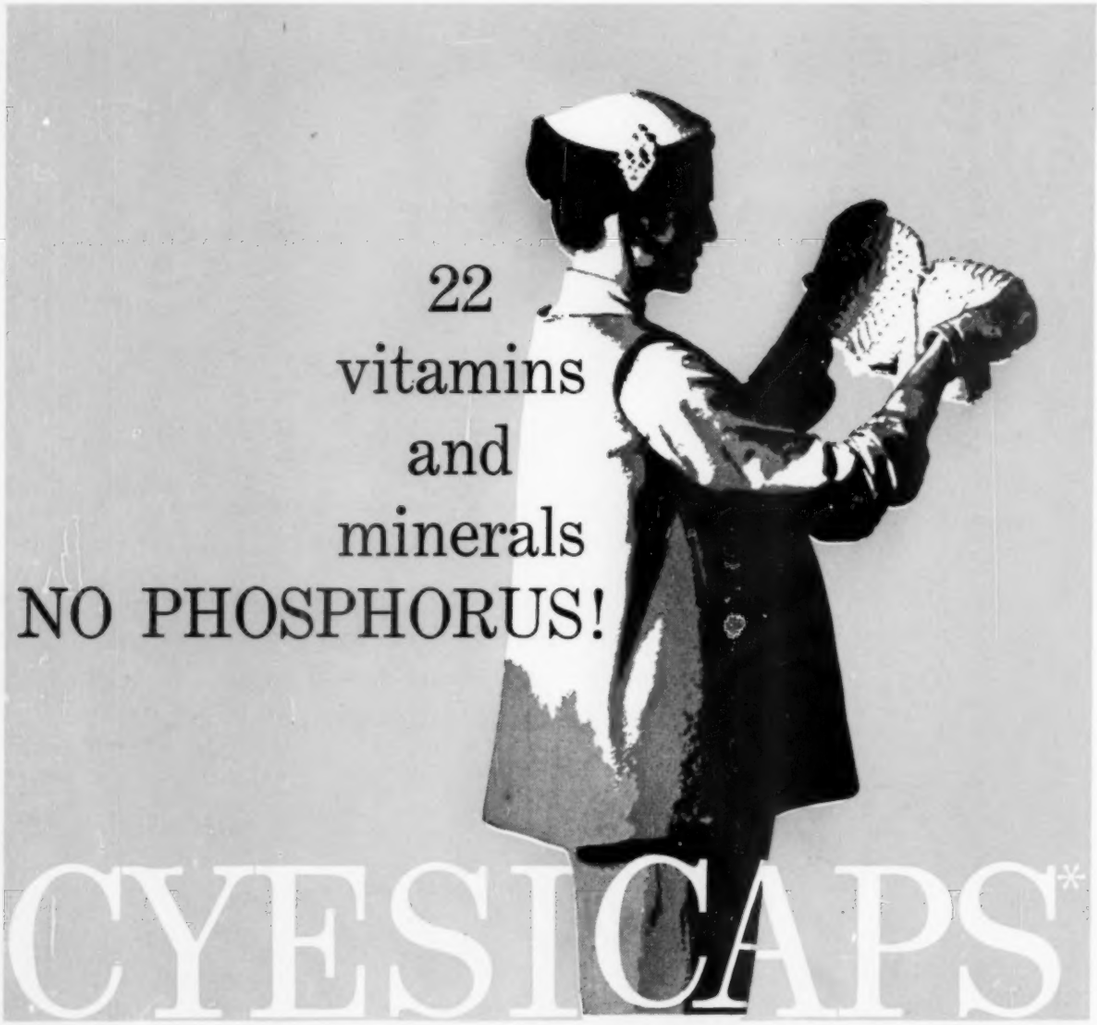
THIOMERIN® Sodium

MERCAPTOMERIN SODIUM



PRENATAL VITAMIN-MINERAL CAPSULES LEDERLE

A single prescription for CYESICAPS assures both mother and child the extra nutrients essential throughout pregnancy and lactation. This phosphorus-free formula includes 12 vitamins, 10 minerals, and purified intrinsic factor concentrate. Calcium is supplied as calcium lactate, its most easily assimilated form.

For maximum effectiveness, for greater patient comfort, CYESICAPS Capsules are *dry-filled* and sealed—a Lederle exclusive. No oils, no paste, no aftertaste!

Dosage: 1 or 2 capsules 3 times daily.

Six capsules supply:

Calcium (as Lactate)	600 mg.
Calcium Lactate	3720 mg.
Intrinsic Factor Concentrate	1.5 mg.
Vitamin A	6,000 U.S.P. Units
Vitamin D	400 U.S.P. Units
Thiamine Mononitrate (B_1)	1.5 mg.
Riboflavin (B_2)	3 mg.
Niacinamide	15 mg.
Vitamin B_{12}	6 mcgm.
Ascorbic Acid	150 mg.
Folic Acid	2 mg.
Pyridoxine HCl (B_6)	6 mg.
Calcium Pantothenate	6 mg.
Vitamin K (Menadione)	1.5 mg.
Iron (as $FeSO_4$ exsiccated)	15 mg.
Vitamin E (as Tocopheryl Acetate)	6 I.U.
Iodine (as KI)	0.1 mg.
Fluorine (as CaF_2)	0.09 mg.
Copper (as CuO)	0.9 mg.
Potassium (as K_2SO_4)	5 mg.
Manganese (as MnO_2)	0.3 mg.
Magnesium (as MgO)	0.9 mg.
Molybdenum (as $Na_2MoO_4.2H_2O$)	0.15 mg.
Zinc (as ZnO)	0.5 mg.

Lederle LEDERLE LABORATORIES DIVISION *AMERICAN CYANAMID COMPANY* PEARL RIVER, NEW YORK

*REG. U.S. PAT. OFF.

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Placidyl

(ETHCHLORVYNOL, ABBOTT)

nudges your patient to sleep

PLACIDYL enables the physician to *induce* sleep instead of *imposing* it. Non-barbiturate. No initial excitation or respiratory depression.

A halogenated carbinol, sold under no other trade name. Abbott

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itching scalp?

scaling scalp?

burning scalp?

Selsun®

relieves seborrheic dermatitis of the scalp and dandruff -quickly, easily, economically.

Just one or two Selsun applications relieve itching, burning scalps. Scaling is completely controlled in 81-87% of seborrheic dermatitis, 92-95% of dandruff cases. And relief lasts—up to four weeks—with each pleasant application. Selsun Suspension is sold only on prescription, in 4-fluidounce bottles with directions.

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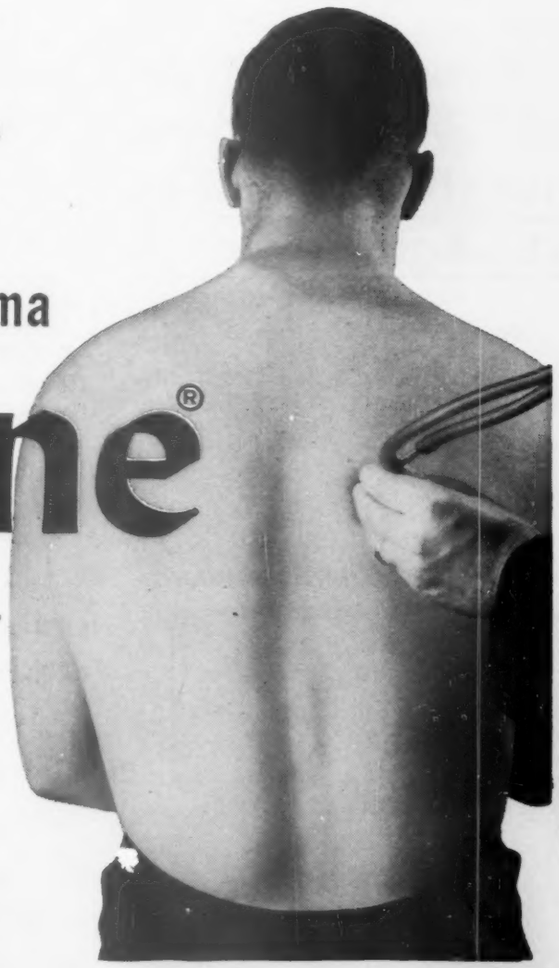
results are obtained with STERANE[1]—3 to 5 times more active than hydrocortisone or cortisone.

BREATHING

capacity is greatly enhanced, "Relief of symptoms is more complete and maintained for longer periods with relatively small doses."[2]

BALANCE

of minerals and fluids usually remains undisturbed. This proves "especially advantageous in those patients with cardiac failure requiring therapy . . ."[3]



in bronchial asthma

Sterane®

brand of prednisolone

Supplied: White, 5 mg. oral tablets, bottles of 20 and 100. Pink, 1 mg. oral tablets, bottles of 100. Both deep-scored.

1. Johnston, T. G., and Cazort, A. G.: J. Allergy 27:90, 1956. 2. Schwartz, E.: New York J. Med. 56:570, 1956. 3. Schiller, I. W., et al.: J. Allergy 27:96, 1956.

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Brooklyn 6, New York

IN WOMEN,

the preferred broad spectrum antibiotic preparation is

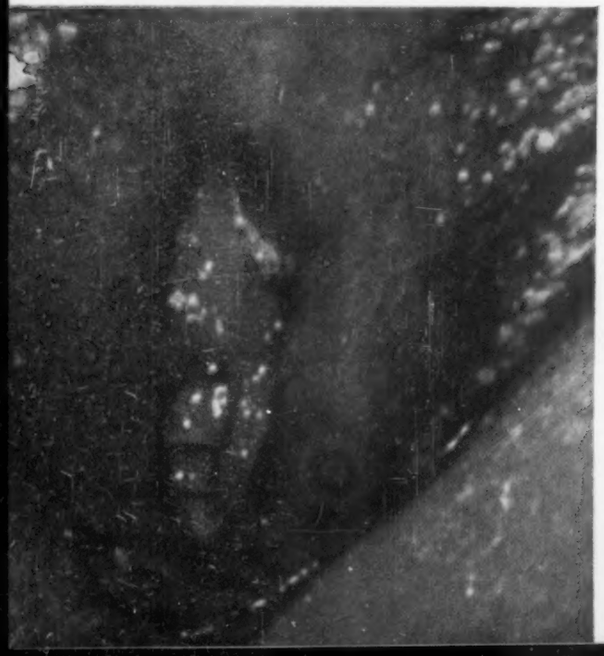
MYSTECLIN

STECLIN-MYCOSTATIN (SQUIBB TETRACYCLINE-NYSTATIN)

Usual broad spectrum antibiotic therapy may be followed by vaginal moniliasis. Mysteclin supplies well tolerated broad spectrum therapy without subsequent vaginal moniliasis.*

*Stone, M. L., and Mersheimer, W. L.: "Comparison of side effects of tetracycline and tetracycline combined with nystatin." Antibiotics Annual 1955-56, New York, Medical Encyclopedia Inc., 1956, p. 862.

Vaginal moniliasis following antibiotic therapy



Oral antibiotic therapy may cause an overgrowth of monilia in the vagina, producing vaginal moniliasis with vulvar pruritus and vaginal discharge. All women are susceptible, but this complication is especially frequent in women who are pregnant or diabetic. In many cases, the woman fails to inform the physician through embarrassment or failure to relate the condition to preceding antibiotic therapy.

SQUIBB

vaginal moniliasis: an increasingly common complication of antibiotic therapy

"... wide use of penicillin and broad spectrum antibiotics, with resultant disturbance of vaginal bacteriology has increased markedly the incidence of yeast and fungus infections of the vagina.... Before advent of the wonder drugs, relationship of trichomonas to monilia was roughly four to one in the usual office practice. Within the past eight years the ratio has been reversed with three monilia problems to one of trichomonas."

Lee, A. F, and Keifer, W. S.:
Northwest Med. 53:1227 (Dec.) 1954.

"Vaginal moniliasis ... is quite common and the incidence may well have been increased following the extensive use of the broad-spectrum drugs or prolonged oral use of penicillin."

Welch, H.: Editorial,
Antibiotic Med. 2:79 (Feb.) 1956.

MYSTECLIN

the only broad spectrum antibiotic preparation that:

1: provides the antibacterial activity of tetracycline and

2: protects the patient against monilial superinfection

Each Mysteclin capsule contains 250 mg. Steclin (Squibb Tetracycline) Hydrochloride, a well tolerated broad spectrum antibiotic, and 250,000 units Mycostatin (Squibb Nystatin), the first well tolerated antibiotic active against fungi. Minimum adult dosage: 1 capsule q.i.d. Supply: Bottles of 16 and 100.

also available: MYSTECLIN Half Strength Capsules (125 mg. Steclin Hydrochloride and 125,000 units Mycostatin): Bottles of 16 and 100.

A PARTIAL LIST OF INDICATIONS FOR MYSTECLIN

When caused by tetracycline-susceptible organisms, the following conditions are among those which may be expected to respond to Mysteclin:

Abscess
Bronchiectasis
Bronchitis
Bronchopneumonia
Burns, Infected
Cellulitis
Cervicitis
Chancroid
Colitis
Cystitis
Diarrheas, Infectious
Dysentery, Amebic
Dysentery, Bacillary
Empyema
Endocarditis, Bacterial
Epididymitis
Furunculosis
Gastroenteritis
Gonorrhea
Granuloma Inguinale
Klebsiella Pneumonia
Laryngitis
Lymphadenitis
Lymphangitis
Lymphogranuloma Venereum
Mastoiditis
Meningitis
Metritis
Osteomyelitis
Otitis Media
Peritonitis
Pertussis
Pharyngitis
Pneumonia
Psittacosis
Pyelonephritis
Q Fever
Rocky Mountain Spotted Fever
Salpingitis
Scarlet Fever
Scrub Typhus
Sepsis, Puerperal
Septic Sore Throat
Septicemia
Sinusitis
Skin Graft Infections
Surgical Prophylaxis
Tonsillitis
Tracheobronchitis
Tularemia
Typhus
Urethritis
Vesiculitis
Wounds, Infected

It is impossible to predict with certainty in which patients clinical moniliasis may develop as a result of broad spectrum antibiotic therapy.

However, the added protection afforded by Mysteclin against monilial superinfection is *especially* important when antibiotic therapy must be prescribed in high dosage or for prolonged periods.

It is also particularly important in women; in debilitated, elderly, or diabetic patients; in infants (particularly prematures); in patients for whom concomitant cortisone or related steroid therapy is prescribed; and in individuals who have developed a monilial complication on previous broad spectrum therapy.

New ganglionic blocker lowers blood pressure consistently, predictably, usually with just 2 oral doses per day

Patients with moderate to severe essential hypertension, and even with malignant hypertension, often respond satisfactorily to a ganglionic blocking agent such as Ecolid. It can be used alone or — for maximal control of blood pressure with minimal side effects — in combination with other antihypertensive agents such as Serpasil or Apresoline.

Advantages

Ecolid has the following advantages over other ganglionic blockers:

- long action, usually requires only two oral doses per day
- rapid absorption — promptly reduces systolic and diastolic pressures
- consistent and predictable response — smoother control
- lower dosage required than with other ganglionic blockers
- minimal likelihood of drug tolerance

Clinical observations

In a study of four ganglionic blocking agents, Winsor[1] found that the "most effective agent was SU3088 [Ecolid]...." In another comparative study, Grimson[2] reported: "Results with Ecolid have been definitely more encouraging than those with pentolinium." Patients maintained on Ecolid state that they prefer this ganglionic blocking agent because of greater energy, improved appetite, less difficulty with constipation and fewer tablets to take.[2,3]

For complete information about Ecolid, particularly more details on dosage recommendations, management of undesired effects and precautions, contact your CIBA representative or write to Medical Service Division for booklet entitled "Ecolid — A New Ganglionic Blocker for Hypertension."

References:

1. Winsor, T.: Am. J. M. Sc. *230*:133 (Aug.) 1955. 2. Grimson, K. S.: J.A.M.A. *158*:359 (June 4) 1955. 3. Grimson, K. S., Tarazi, A. K., and Frazer, J. W., Jr.: Circulation *11*:733 (May) 1955. 4. Grimson, K. S., Tarazi, A. K., and Frazer, J. W., Jr.: Angiology *6*:507 (Dec.) 1955. 5. Strawn, J. R., and Moyer, J. H.: Personal communication, 1955. 6. Maxwell, R. D. H., and Howie, T. J. G.: Brit. M. J. *2*:1189 (Nov. 12) 1955.

SUPPLIED: ECOLID Tablets (Rotocotes), 25 mg. (ivory) and 50 mg. (pink).

DOSAGE: Dosage must be adjusted to the individual patient. Below is a typical plan by which treatment may be initiated.

Ambulatory patients		
DAY	A.M.	P.M.
1	25 mg.	—
2	25 mg.	25 mg.
3	50 mg.	25 mg.
4	50 mg.	50 mg.
5	75 mg.	50 mg.
6	75 mg.	75 mg.
7	100 mg.	75 mg.
8	100 mg.	100 mg.

Hospitalized patients		
DAY	A.M.	P.M.
1	50 mg.	—
2	50 mg.	50 mg.
3	100 mg.	50 mg.
	100 mg.	100 mg.
to optimal response		

Ecolid T.M.

chloride

(chlorisondamine chloride CIBA)

SERPASIL® (reserpine CIBA)
APRESOLINE® hydrochloride (hydralazine hydrochloride CIBA)
ROTOCOTES T.M. (dry-compressed, coated tablets CIBA)

REPRESENTATIVE CLINICAL STUDIES OF Ecolid*

Number of Patients	Initial Oral Dosage	Responses	Duration of Action	References
59 (Total Series)	75 to 300 mg. daily	Compared with other ganglionic blockers, small doses of Ecolid were employed and greater hypotensive effect was obtained. Rapid absorption and long duration of hypotensive action.	Postural hypotension lasted 13.4 hours in 5 "test" patients receiving doses of 150 mg.	1
20	50 to 200 mg. daily	Blood pressure in 20 well controlled; reductions lasted twice as long as those induced by pentolinium. Each of 10 patients with previous experience with hexamethonium preferred Ecolid. Less difficulty with constipation; appetite improved; greater energy.	**	2
18	50 to 100 mg. daily	Hypertension in 18 well controlled. Supine blood pressure reduced without tachycardia. Constipation occurred infrequently.	Supine blood pressure lowered for 12 hours or more with single oral doses of 50 to 100 mg.	3,4
44	50 mg. daily	35 responded well; 14 of these became normotensive. All patients received reserpine as base therapy.	**	5
12	25 to 200 mg. daily	Blood pressure of all 12 satisfactorily controlled. Systolic blood pressure lowered average of 76 mm. Diastolic blood pressure lowered average of 42 mm.	**	6

*To date, a total of 63 investigators have reported on the use of Ecolid in more than 500 patients. They were practically unanimous in the opinion that Ecolid was highly effective. Nearly all commented on the prolonged duration of action—about 8 to 12 hours—which permitted a twice daily dosage schedule in most cases.

**Information not available.

SUMMIT, N. J.

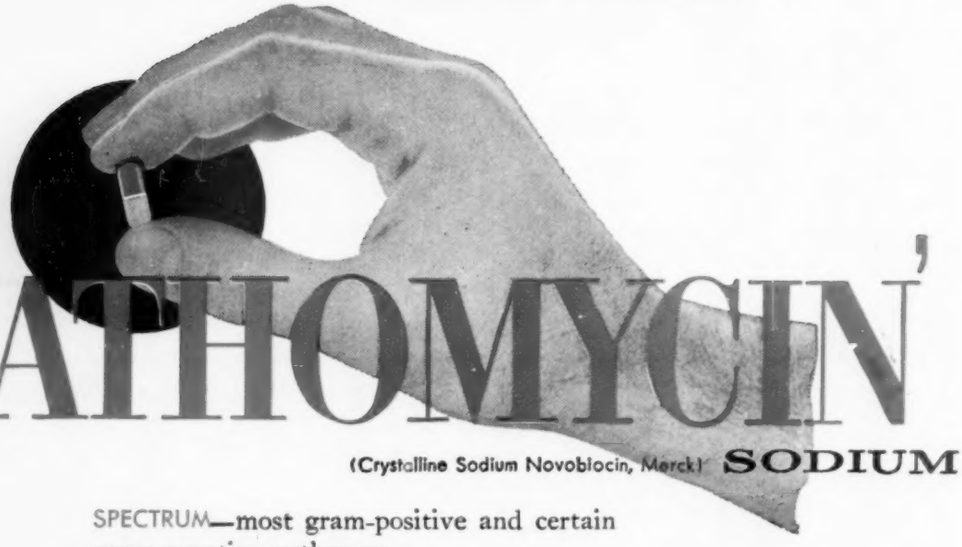
2/2251M

NOW AVAILABLE...

a unique new antibiotic of major importance

PROVED EFFECTIVE AGAINST SPECIFIC ORGANISMS
(staphylococci and proteus)

RESISTANT TO ALL OTHER ANTIMICROBIAL AGENTS



'CATHOMYCIN' SODIUM

(Crystalline Sodium Novoblocin, Merck)

SPECTRUM—most gram-positive and certain gram-negative pathogens.

ACTION—bactericidal in optimum concentration even to resistant strains.

TOXICITY—generally well tolerated. This is more fully discussed in the package insert.

ABSORPTION—oral administration produces high and easily-maintained blood levels.

INDICATIONS—cellulitis, pyogenic dermatoses, septicemia, bacteremia, pneumonia and enteritis due to *Staphylococcus* and infections involving certain strains of *Proteus vulgaris;* including strains resistant to all other antibiotics.

DOSAGE—four capsules (one gram) initially and then two capsules (500 mg.) twice daily.

SUPPLIED—250 mg. capsules of 'CATHOMYCIN', bottles of 16.

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A FIRST THOUGHT IN HYPERTENSION
EVERY GRADE...
EVERY TYPE

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original alseroxylon	all the desirable alkaloids of India-grown Rauwolfia serpentina, Benth.
mutually potentiated action	high clinical efficacy because of interpotentiation of contained alkaloids
freed from undesirable alkaloids	yohimbine-like and other undesirable substances in the Rauwolfia root are removed
virtually no serious side actions	when side actions are encountered, they are notably mild
especially suitable for long-term therapy	no alteration in patients' tolerance, no chronic allergic toxicity, no latent undesirable actions
easy to prescribe	simple regimen—merely two 2mg. tablets at bedtime; for maintenance 1 tablet usually suffices.

ZIRADRYL®

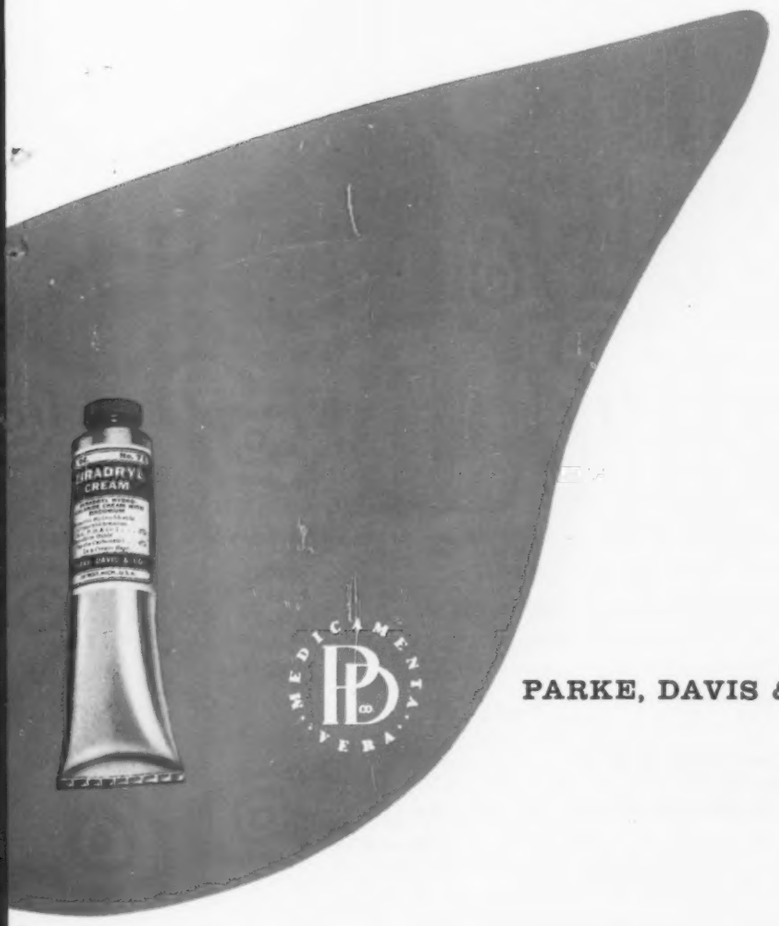
Benadryl® Hydrochloride with Zirconium

now available in Lotion

as well as in Cream form

ZIRADRYL Cream and ZIRADRYL Lotion are compounded to aid in the prevention and treatment of poison ivy and poison oak dermatitis. ZIRADRYL contains Benadryl which controls the allergic process by relieving itching, and also contains zirconium oxide, which neutralizes the plant toxin.

ZIRADRYL Cream is available in 1-ounce tubes.
ZIRADRYL Lotion is available in 6-ounce bottles.



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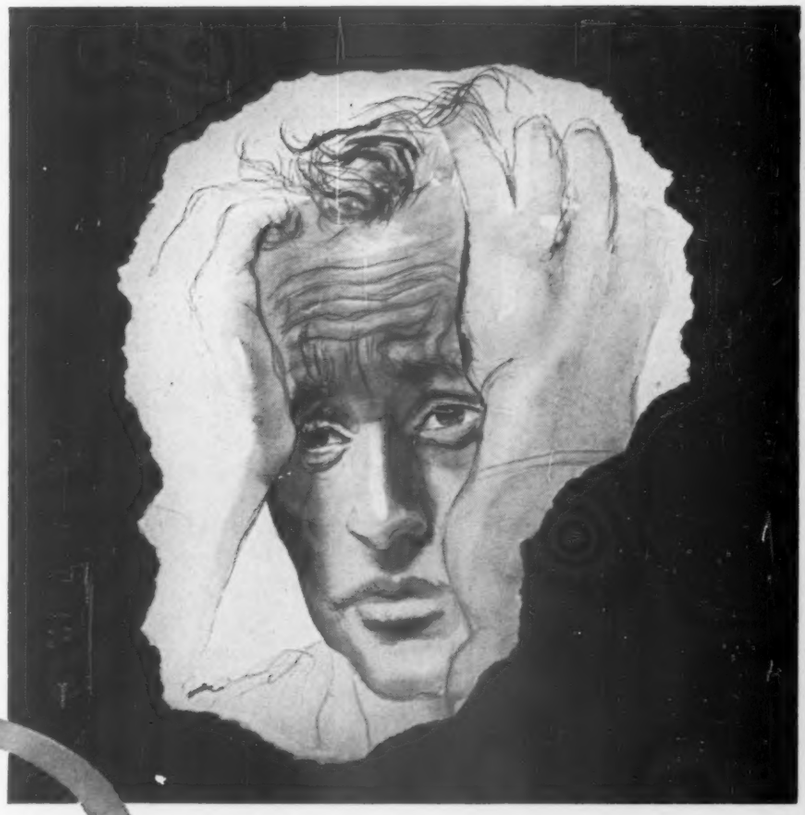

for a sound sleep tonight, a calm day tomorrow . . .

filmtab

Nembu-Serpin®

Restful nights are added to calm days for anxiety and mild hypertension patients when you prescribe Nembu-Serpin. The 30 mg. (½ gr.) of short-acting Nembutal (Pentobarbital Calcium) in each tiny Filmtab quickly induces drowsiness at bedtime, followed by refreshing sleep. Then the 0.25 mg. of longer-acting reserpine in each Filmtab calms patients all through the following days.

Patients experience almost immediate relief as Nembu-Serpin's sedative-tranquilizing action rapidly takes effect. Then their sense of well-being increases during the following few days. Nembu-Serpin avoids prolonged waiting for a cumulative response to reserpine.

Small dosages add safety, simplicity, economy for patients. Dosage schedules are simple, medication economical: just one Nembu-Serpin Filmtab at bedtime will calm the worries of most anxiety patients.
Nembu-Serpin Filmtabs—in bottles of 100 and 500.

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●*Film-sealed tablets*

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a new substance

in a variety of rheumatic disorders...

"an 85% over-all effectiveness"[1]

the first orally effective lissive[‡]

three or four times
tablet two to four ti

lets (250 mg.), bottles o

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for true spasmolysis
of skeletal muscle

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through-the-night photographs show...

NONBARBITURATE

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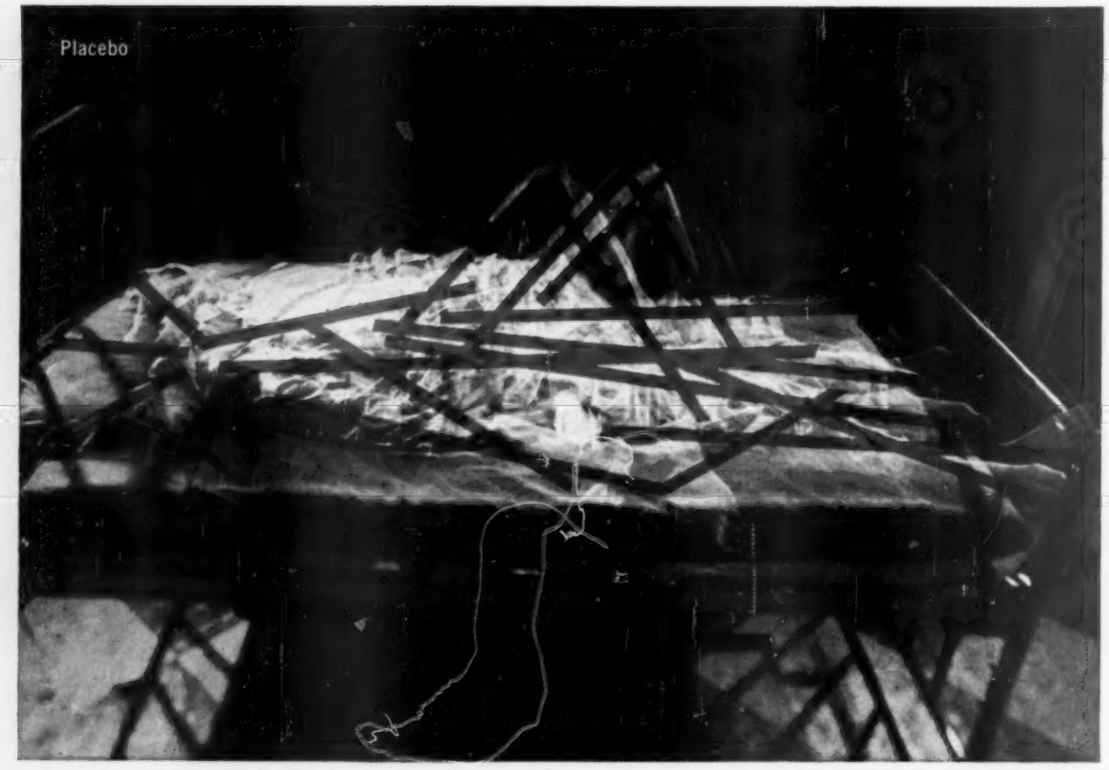
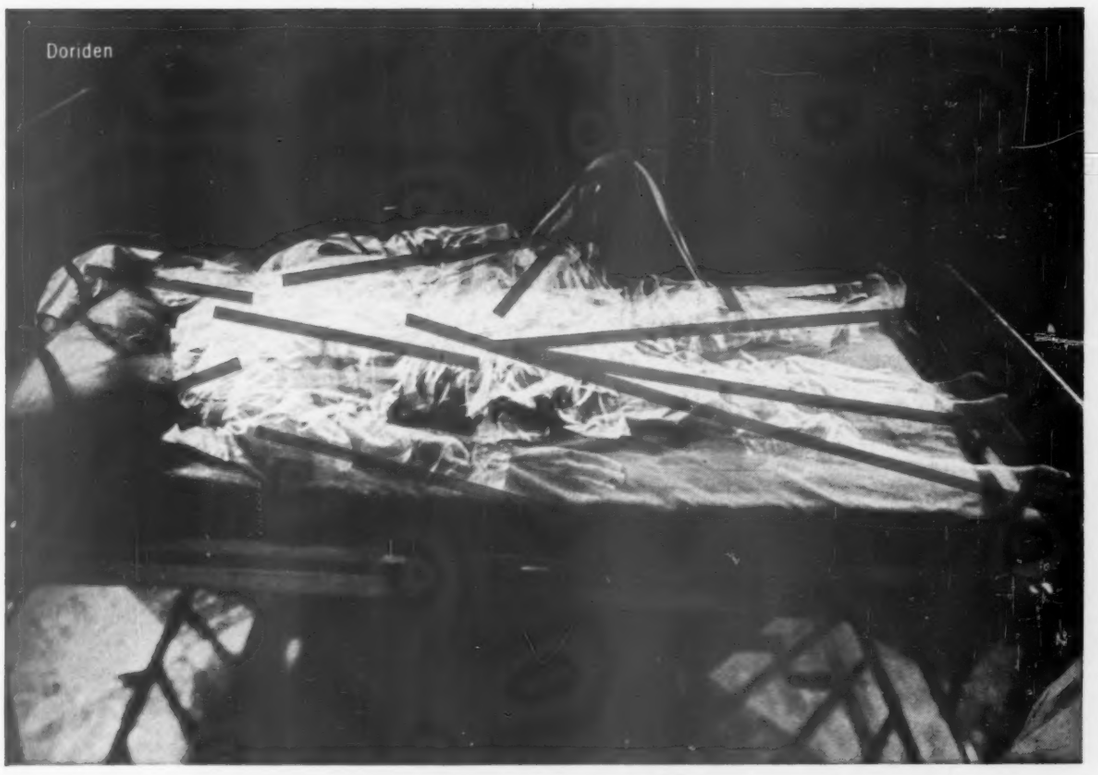


Twenty-eight-year-old male, restless sleeper, tense personality with occasional insomnia, was photographed at fixed intervals during the night to produce a series of exposures on same sheet of film. On placebo (above), unique "stroboscopic" picture shows him in typical fitful night of unrest.

Further clinical evidence of the sedative and hypnotic effectiveness of DORIDEN is provided by numerous clinical studies. In most cases, Doriden acts in 15 to 30 minutes, affords 4 to 8 hours of refreshing sleep... and come morning, the patient awakens "clear-headed."

induces sound, restful sleep



Same patient on successive night, following administration of Doriden 0.5 Gm. at bedtime, is shown in distinctly more restful repose. Total sleep was achieved in 16 minutes. Close study of activity pattern shows approximately 50 per cent reduction in overt motion and restlessness.

DORIDEN is also an excellent daytime sedative... calms the tense, anxious, overwrought patient.

DOSAGE: For SLEEP—0.5 Gm. at bedtime.
As a DAYTIME SEDATIVE—0.125 or 0.25 Gm. t.i.d. after meals.

TABLETS, 0.125 Gm., 0.25 Gm. (scored) and 0.5 Gm. (scored).

DORIDEN® (glutethimide CIBA)

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blue at breakfast?

BONADOXIN®

stops morning sickness

90-95% effective,[1-2] "no side effects were observed"[2] one tablet at bedtime

1. Groskloss, H. H. et al: Bonadoxin®: a unique control for nausea and vomiting of pregnancy. Clin. Med. 2:885 (Sept.) 1955. 2. Tartikoff, G.: The antiemetic function of Bonadoxin in the nausea and vomiting of pregnancy. Clin. Med. 3:223 (Mar.) 1956.

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Against Disease and Discomfort

in urinary tract infections

Azo Gantrisin, in one tablet, combines Gantrisin with a widely-used urinary tract analgesic. The high plasma and urine levels achieved by Gantrisin effectively combat urinary infections both systemically and locally. The rapid local action of the analgesic dye is reflected by the early appearance of an orange-red color in the urine. Each Azo Gantrisin tablet contains 0.5 Gm Gantrisin 'Roche' plus 50 mg phenylazo-diamino-pyridine HCl.

Gantrisin® - brand of sulfisoxazole

'Roche' | Original Research in Medicine and Chemistry

For patients harried by hurry and worry —

Noludar 'Roche' brings calm and quiet. Not a barbiturate, not habit forming, 50 mg t.i.d. provides daytime sedation with little or no loss of acuity, or 200 mg h.s. induces a sound night's sleep with a refreshed and clear-headed awakening. Noludar tablets, 50 and 200 mg; elixir, 50 mg per teaspoonful. Hoffmann-La Roche Inc, Nutley, New Jersey.

Noludar® brand of methyprylon

a "judicious combination..."

for antiarthritic therapy

SALCORT*

That cortisone and the salicylates have a complementary action has been well established.[1-5] In rheumatic conditions, functional improvement and a sense of feeling well are noted early. No withdrawal reactions have been reported.

One clinician states: "By a judicious combination of the two agents . . . it has been possible to bring about a much more favorable reaction in arthritis than with either alone. Salicylate potentiates the greatly reduced amount of cortisone present so that its full effect is brought out without evoking undesirable side reactions."[1]

INDICATIONS:

Rheumatoid arthritis . . . Rheumatoid spondylitis . . . Rheumatic fever . . . Bursitis . . . Still's disease . . . Neuromuscular affections

EACH TABLET CONTAINS:

Cortisone acetate	2.5 mg.
Sodium salicylate	0.3 Gm.
Aluminum hydroxide gel, dried .	0.12 Gm.
Calcium ascorbate	60 mg.
(equivalent to 50 mg. ascorbic acid)	
Calcium carbonate	60 mg.

* U.S. Pat. 2,691,662

1. Busse, E.A.: Treatment of Rheumatoid Arthritis by a Combination of Cortisone and Salicylates. Clinical Med. 11:1105 (Nov., 1955).
2. Roskam, J., VanCawenberge, H.: Abst. in J.A.M.A., 151:248 (1953).
3. Coventry, M.D.: Proc. Staff Meet., Mayo Clinic, 29:60 (1954).
4. Holt, K.S., et al.: Lancet, 2:1144 (1954).
5. Spies, T.D., et al.: J.A.M.A., 159:645 (Oct. 15, 1955).

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ACHROMYCIN

Tetracycline *Lederle*

in the treatment of

infections in surgery

The prevention and control of cellulitis, abscess formation, and generalized sepsis has become commonplace technique in surgery since ACHROMYCIN has been available. Leading investigators have documented such findings in the literature.

For example, Albertson and Trout[1] have reported successful results with tetracycline (ACHROMYCIN) in diverticulitis, gangrene of the gall bladder, tubo-ovarian abscess, and retropharyngeal abscess. Prigot and his associates[2] used tetracycline in successfully treating patients with subcutaneous abscesses, cellulitis, carbuncles, infected lacerations, and other conditions.

As a prophylactic and as a therapeutic, ACHROMYCIN has shown its great worth to surgeons, as well as to internists, obstetricians, and physicians in every branch of medicine. This modern antibiotic offers rapid diffusion and penetration, quick development of effective blood levels, prompt control over a wide range of organisms, minimal side effects. There are 21 dosage forms to suit every need, every patient, including

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ACHROMYCIN with STRESS FORMULA VITAMINS. Broad-range antibiotic action to fight infection; important vitamins to help speed normal recovery. In *dry-filled, sealed* capsules for rapid and complete absorption, elimination of aftertaste.

dry-filled sealed capsules

[1]Albertson, H.A. and Trout, H. H., Jr.: *Antibiotics Annual* 1954-55, Medical Encyclopedia, Inc., New York, N.Y., 1955, pp. 599-602.

[2]Prigot, A.; Whitaker, J. C.; Shidlovsky, B. A., and Marmell, M.: *ibid*, pp. 603-607.

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Each SUR-BEX with C tablet contains:

Thiamine Mononitrate	6 mg.
Riboflavin	6 mg.
Nicotinamide	30 mg.
Pyridoxine Hydrochloride	1 mg.
Vitamin B_{12} *(as cobalamin concentrate)*	2 mcg.
Calcium Pantothenate	10 mg.
Ascorbic Acid	150 mg.
Liver Fraction 2, N. F.	300 mg. (5 grs.)
Brewer's Yeast, Dried	150 mg. (2½ grs.)

As a dietary supplement: 1 or 2 tablets daily.

For stress, or postoperative convalescence: 2 or more tablets daily.

607206

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clinically proved in many common infections[1-60]

Hemolytic streptococcal infections
- Pharyngitis
- Tonsillitis
- Sinusitis
- Otitis media
- Mastoiditis
- Scarlet fever
- Lymphadenitis
- Erysipelas

Staphylococcal infections
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Vincent's infection
Prevention of streptococcal infection in individuals with a history of rheumatic fever
Prevention of secondary infection due to penicillin-susceptible organisms

in dosage of just 1 or 2 tablets t.i.d.

Pentids

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Recommended dosage: 1 or 2 tablets t.i.d. without regard to meals. Bottles of 12 and 100.

References: 1. Boger, W. P., J. Amer. Ger. Soc. 1:556, Aug. 1955. 2. Lepin, J. H., Ann. Allergy 13:169, March-April 1955. 3. Andelman, M. B. and Fischbein, W. I., Antibiotic Med. 1:136, March 1955. 4. Statements of American Heart Association, Council on Rheumatic Fever and Congenital Heart Disease, Circulation 11: 317, Feb. 1955. 5. Miller, J. M. et al., Antibiotics Annual 1954-55, Medical Encyclopedia Inc., N.Y., p. 105. 6. Seal, J. R. et al., J. Lab. & Clin. Med. 44:831, Dec. 1954. 7. Martin, W. J. et al., Am. Pract. & Dig. Treat. 5:813, Oct. 1954. 8. Henner, R., Eye, Ear, Nose & Throat Monthly 33:530, Sept. 1954. 9. Rodstein, M. and Young, D., Clin. Med. 61:695, Sept. 1954. 10. Bernstein, S. H. et al., A. M. A. Arch. Int. Med. 93: 894, June 1954. 11. Craige, E., North Carolina M. J. 14:523, Dec. 1953. 12. Barach, A. L., J. Amer. Ger. Soc. 1:616, Sept. 1953. 13. Barach, A. L., Geriatrics 8:423, Aug. 1953. 14. Boger, W. P., Indus. Med. & Surg. 22:288, July 1953. 15. Young, D. and Rodstein, M., J.A.M.A. 152:987, July 1953. 16. Queries and Minor Notes, J.A.M.A. 152:1083, July 1953. 17. Roberts, E., A. M. A. Amer. J. Dis. Child. 85:643, June 1953. 18. Spink, W. W., J.A.M.A. 152:585, June 1953. 19. Huang, N. N. and High, R. H., J. Pediat. 42:532, May 1953. 20. Antibiotics: Round Table Discussion, Pediatrics 11:270, March 1953. 21. Feinberg, B., Rhode Island M. J. 36:138, March 1953. 22. Flippin, H. F., Delaware State M. J. 25:55, March 1953. 23. Denny, F. W. Jr., Postgrad. Med. 13:153, Feb. 1953. 24. Flood, J. M., A. M. A. Arch. Dermat. & Syph. 67:42, Jan. 1953. 25. Konn, K. H., Milzer, A. and MacLean, H., J.A.M.A. 151:347, Jan. 1953. 26. Siegal, S. et al., J. Allergy 24: 1, Jan. 1953. 27. Statements of American Heart Association, Council on Rheumatic Fever and Congenital Heart Disease, J.A.M.A. 151:141, Jan. 1953. 28. Keefer, C. S., Pennsylvania M. J. 55:1177, Dec. 1952. 29. Kerrell, W. E., J.A.M.A. 150:1450, Dec. 1952. 30. Levy, D. F., Connecticut State M. J. 16:899, Dec. 1952. 31. Romansky, M. J. and Kelser, G. A., J.A.M.A. 150: 1447, Dec. 1952. 32. Thomas, L., Minnesota Med. 35: 1105, Dec. 1952. 33. Jones, C. C., J. Iowa M. Soc. 42: 533, Nov. 1952. 34. Reimann, H. A. Postgrad. Med. 12:255, Sept. 1952. 35. Bunn, P. A., N. Y. State J. Med. 52:2005, Aug. 1952. 36. Finland, M., New England J. Med. 247:557, Oct. 1952. 37. Babione, R. W. et al., U. S. Armed Forces M. J. 3:973, July 1952. 38. Hansen, A. E., South. M. J. 45:423, May 1952. 39. Dowling, H. F., G. P. 5:53, Feb. 1952. 40. Rhoades, P. S., G. P. 5:67, Feb. 1952. 41. Dowling, H. F. and Lepper, M. H., Med. Clin. North Amer., Jan. 1952, p. 247. 42. Kereiitz, S. and Schiffin, N., Postgrad. Med. 11:17, Jan. 1952. 43. Panel Discussion, Pennsylvania M. J. 55:12, Jan. 1952. 44. Flippin, H. F. et al., J.A.M.A. 147:918, Nov. 1951. 45. Massell, B. F., Mod. Concepts Cardiovas. Dis. 20:105, Sept. 1951. 46. Weinstein, L., Boston Med. Quarterly 2:1, Sept. 1951. 47. Massell, B. F. et al., J.A.M.A. 146:1469, Aug. 1951. 48. Finland, M., Bull. New York Acad. Med. 27:199, April 1951. 49. Wheatley, D., Brit. M. J. 1: 703, March 1951. 50. Keefer, C. S., Postgrad. Med. 9:101, Feb. 1951. 51. Bunn, P. A. et al., J.A.M.A. 144: 1540, Dec. 1950. 52. Wainstein, L. and Perrin, T. S., J. Pediat. 47:844, Dec. 1950. 53. Keefer, C. S., Am. J. Med. 7:216, Aug. 1949. 54. Robinson, J. A., Hirsch, H. L. and Dowling, H. F., Am. J. Med. 4:718, 1948. 55. Barach, A. L. and Garthwaite, B., Ann. Allergy 5: 297, Aug. 1947. 56. Herrold, R. D., J. Urol. 57:897, May 1947. 57. White, H. J., Lee, M. E. and Alverson, C., Proc. Soc. Exper. Biol. & Med. 62:35, 1946. 58. Baumann, F. et al., J. Allergy 17:264, Sept. 1946. 59. Gamble, T. O. et al., Am. J. Obst. & Gynec. 50: 514, Nov. 1945. 60. Woolfer, A. C. and Hoffman, O. E., J. Iowa M. Soc. 35:139, May 1945.

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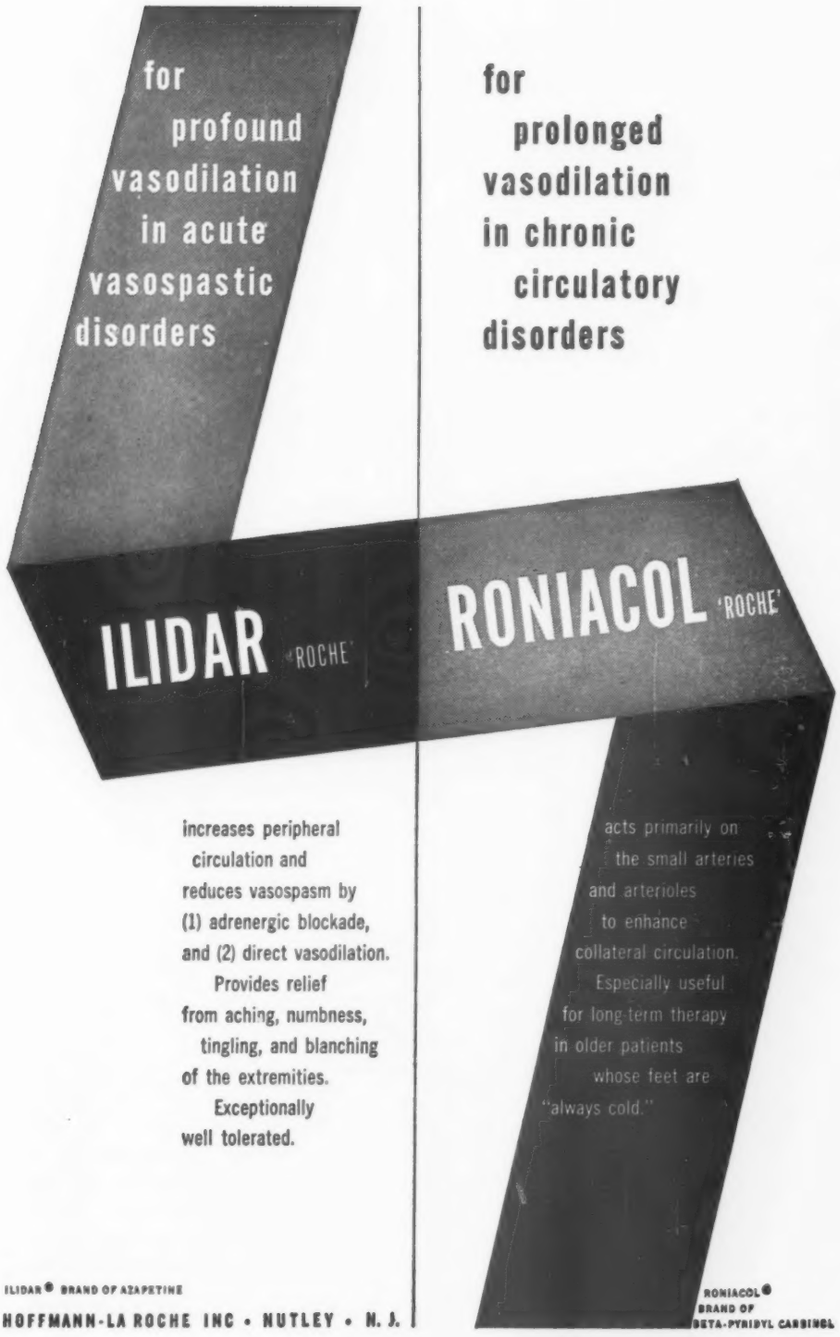
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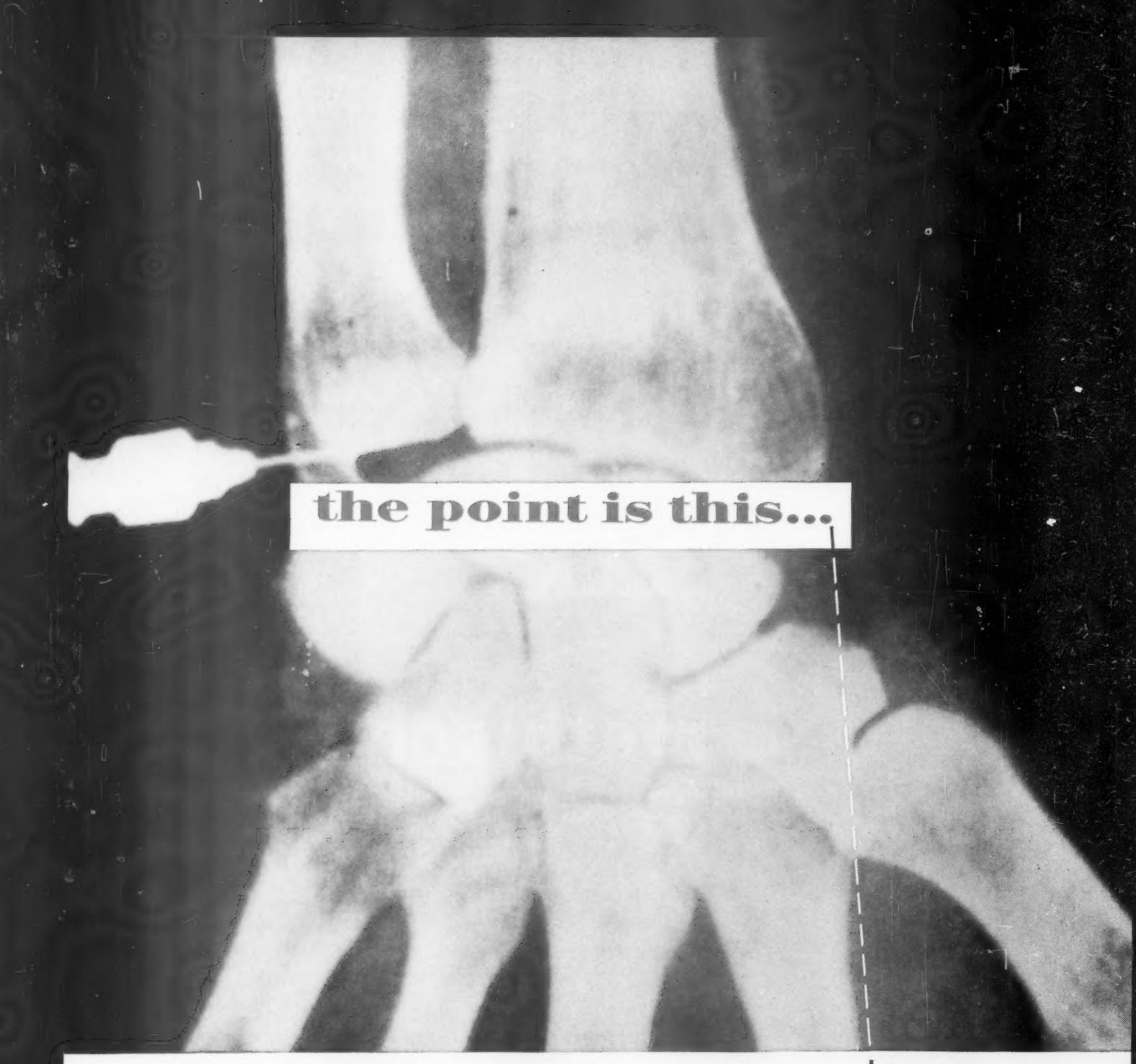
Xylocaine HCl Solutions are available in 2 cc. ampuls, 20 cc. and 50 cc. vials in strengths of 0.5%, 1% and 2%, with or without epinephrine.

Bibliography of approximately 300 Xylocaine references upon request.

*Southworth, J. L., and Dabbs, C. H.: Xylocaine: a superior agent for conduction anesthesia, Anesth. & Analg. *32*:159 (May-June) 1953.

Astra Pharmaceutical Products, Inc., Worcester 6, Mass.



HydroCortone® -T.B.A.

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produces superior results — greater symptomatic relief and longer-lasting remissions — in both rheumatoid arthritis and osteoarthritis.

SUPPLIED: SALINE SUSPENSION HYDROCORTONE-T.B.A.—25 MG./CC., VIALS OF 5 CC.

References: 1. Hollander, J. L., *Ann. New York Acad. Sc.* **61**:511, May 27, 1955.
2. Hollander, J. L., *et al. J.A.M.A.* **158**:476, June 11, 1955.

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METHISCHOL helps to terminate this vicious cycle . . . by acting to increase phospholipid turnover, to reduce fatty deposits and fibrosis of the liver, to stimulate regeneration of new liver cells . . . and generally to help improve liver function.

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The desirable hypotensive action of reserpine is often accompanied by distressing side effects. These include nasal congestion, hyperperistalsis, nightmares and mental depression.

Renir, which provides the desired action of reserpine, counterbalanced by the well-known effects of ephedrine, offers the optimum in hypotensive therapy. Untoward reactions are minimized, and tranquilization is maintained.

Investigators state that: ". . . with reserpine and ephedrine, the untoward effects of each are counteracted and the desirable effects of each are enhanced."[1]

INDICATIONS: In the treatment of mild, moderate and labile hypertension. Also anxiety and tension states; mild to severe neurosis.

SUGGESTED DOSAGE: For hypertension, 1 to 3 tablets daily. As a tranquilizer in mentally disturbed states, 2 to 4 tablets daily.

SUPPLIED: Tablets containing reserpine 0.25 mg., and ephedrine 8.0 mg., in bottles of 100.

CONTRAINDICATIONS: To be used with caution in patients with peptic ulcer, mental depression, cardiac conditions and related disorders.

LITERATURE AND SAMPLES ON REQUEST.

1. *Feinblatt, T.M., Feinblatt, H.M., and Ferguson, E.A.: Rauwolfia-Ephedrine, A Superior Hypotensive-Tranquilizer. In press.*

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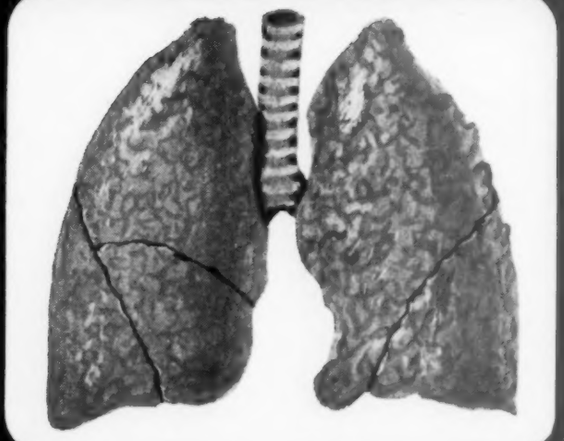
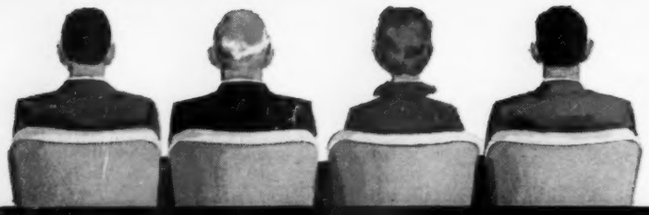
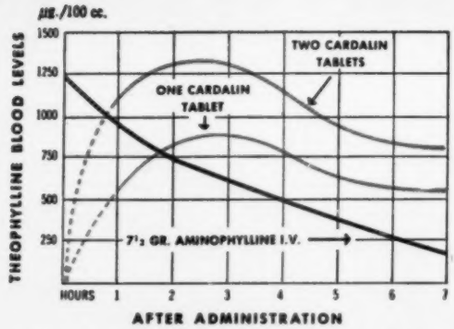
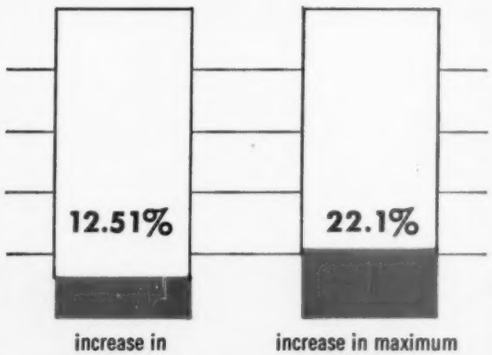




2. Cardalin (protected aminophylline) can make therapy safer in severe asthma.



(Adapted from Bickerman, H. A., et al.: Ann. Allergy 11: 301, 1953, and Truitt, E. B., Jr., et al.: J. Pharmacol. & Exper. Therap. 100: 309, 1950.)



5. Cardalin works by producing high, sustained theophylline blood levels within an hour,

6. thereby increasing the asthmatic's vital capacity and maximum breathing capacity.

Concurrent therapy with CARDALIN can minimize these risks of corticoid therapy:

- **activation and perforation of gastric ulcers**
- **water and salt retention**
- **nervous tension and undue mental stimulation**

3. Concurrent therapy with Cardalin can reduce the effective dose of corticoids, avoid overdosage effects . . .

4. and lead to: safer control of asthma • quicker remissions • fewer side effects • faster discontinuance of corticoids and less costly treatment.

How Cardalin can reduce dosage of corticoids

1 Begin with prednisone*—15 mg. q.i.d. and 1 Cardalin tablet before breakfast, at 4 p.m. and at bedtime.

2 After severe symptoms are relieved (2nd or 3rd day) reduce the dose of prednisone* to 10 mg. q.i.d.; continue Cardalin dosage.

3 After remission occurs (slight or no asthma) reduce the dose of prednisone to 5 mg. q.i.d.; give 1 Cardalin tablet morning and at bedtime.

Reduce prednisone dosage 5 mg. each week, attempting to discontinue its use. Continue Cardalin at reduced dosage level (1 tablet, morning and at bedtime).

*or any corticoid of your choice, in appropriate dosage.

℞ Cardalin TABLETS

Each tablet contains:

Aminophylline	5.0 gr.
Aluminum hydroxide	2.5 gr.
Ethyl aminobenzoate	0.5 gr.

Also available, Cardalin-Phen, containing in addition, ¼ gr. phenobarbital per tablet.

You can give a full therapeutic dose of aminophylline orally with Cardalin tablets. Two protective factors—aluminum hydroxide and ethyl aminobenzoate—effectively minimize gastric irritation so common with other forms of aminophylline, and also with corticoids.

7. As a result, a smaller amount of corticoids need be given and asthma therapy is made safer and more economical.

8. Look for further details in your mail this month!

IRWIN, NEISLER & COMPANY • DECATUR, ILLINOIS

introducing . . .

'CORTISPORIN'® *brand*

OTIC DROPS *Sterile*

to relieve bacterial or allergic otitis

when inflammation is prominent

gives prompt relief of:

inflammation,

edema,

exudation,

pruritus,

pain,

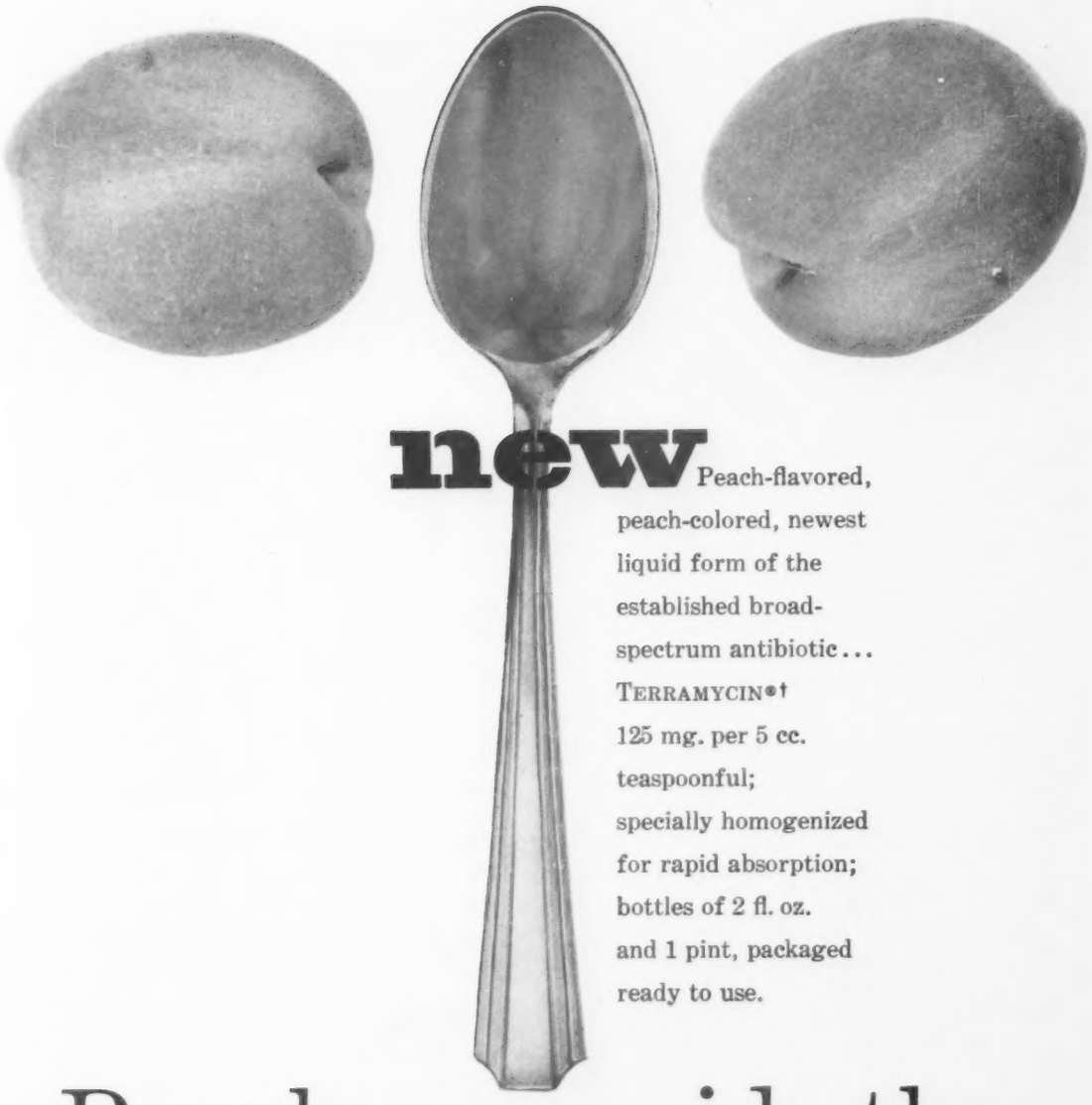
and early eradication of:

gram-positive and

gram-negative bacteria

containing: 'Aerosporin'® Sulfate Polymyxin B Sulfate, Neomycin Sulfate and Hydrocortisone (free alcohol).

BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, New York



new Peach-flavored, peach-colored, newest liquid form of the established broad-spectrum antibiotic... TERRAMYCIN®† 125 mg. per 5 cc. teaspoonful; specially homogenized for rapid absorption; bottles of 2 fl. oz. and 1 pint, packaged ready to use.

Peaches provide the delightful new taste in TERRABON®

BRAND OF OXYTETRACYCLINE

HOMOGENIZED MIXTURE

PFIZER LABORATORIES, *Division, Chas. Pfizer & Co., Inc.*, Brooklyn 6, N. Y. Pfizer

†Brand of oxytetracycline

Newest in vitamin therapy

Vitamins as nature intended . . .

HOMAGENETS©

THE HOMOGENIZED VITAMINS

For the first time, all the advantages of multivitamin drops are available in a tablet. By a unique process, the vitamins are homogenized, then fused into a solid, highly palatable form.

As a result of this minute subdivision, the vitamins are absorbed and utilized much more efficiently than those in the usual compressed tablet or elastic capsule.

- Better absorbed and utilized
- Pleasant, candy-like flavor
- No regurgitation, no "fishy burp"
- May be chewed, swallowed, or dissolved in the mouth

Three formulas:

Prenatal
Pediatric
Therapeutic

*U.S. Patent 2676136

The S. E. MASSENGILL COMPANY
Bristol, Tennessee
New York • Kansas City • San Francisco

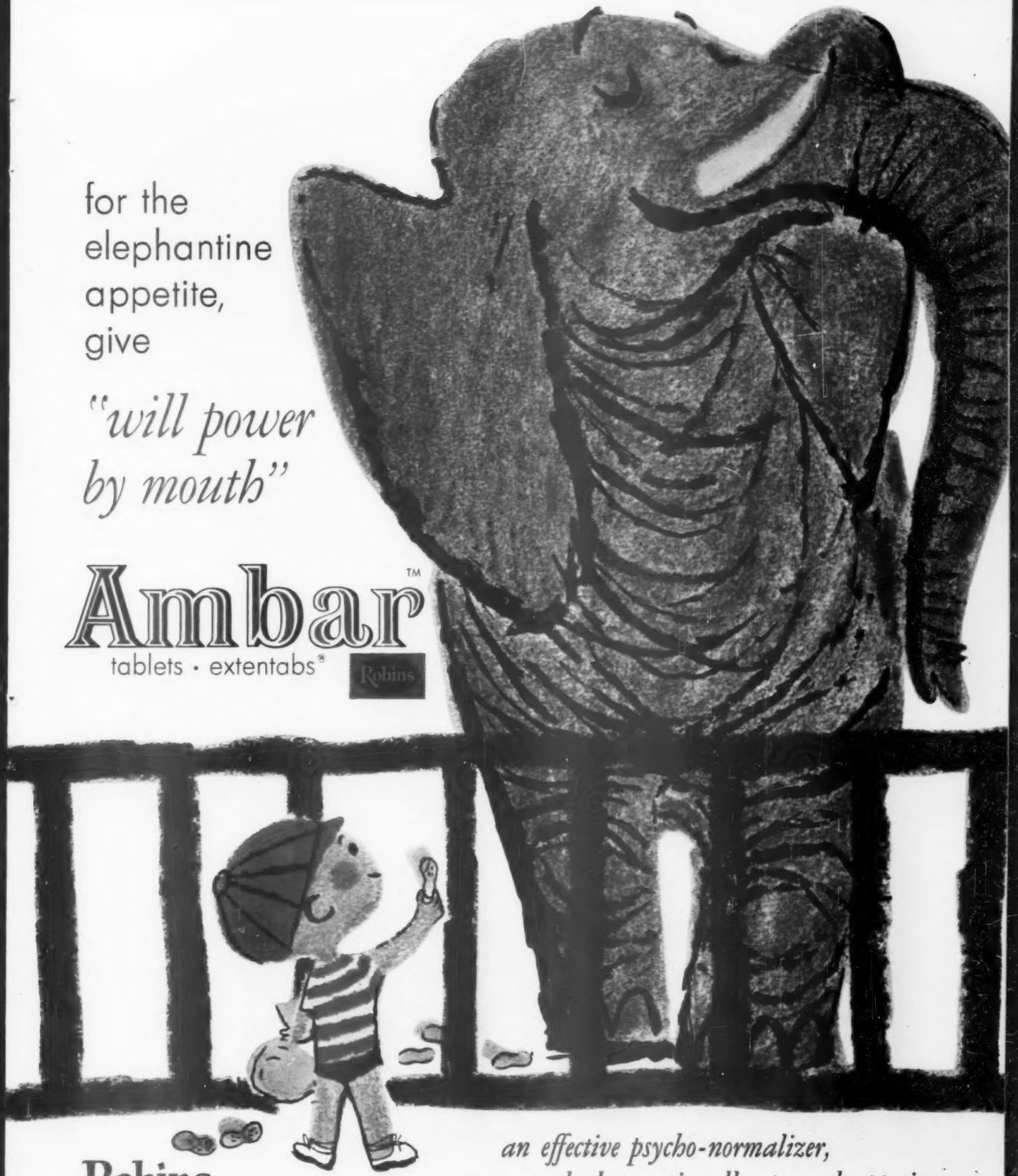
for the
elephantine
appetite,
give

*"will power
by mouth"*

Ambar™

tablets · extentabs®

Robins



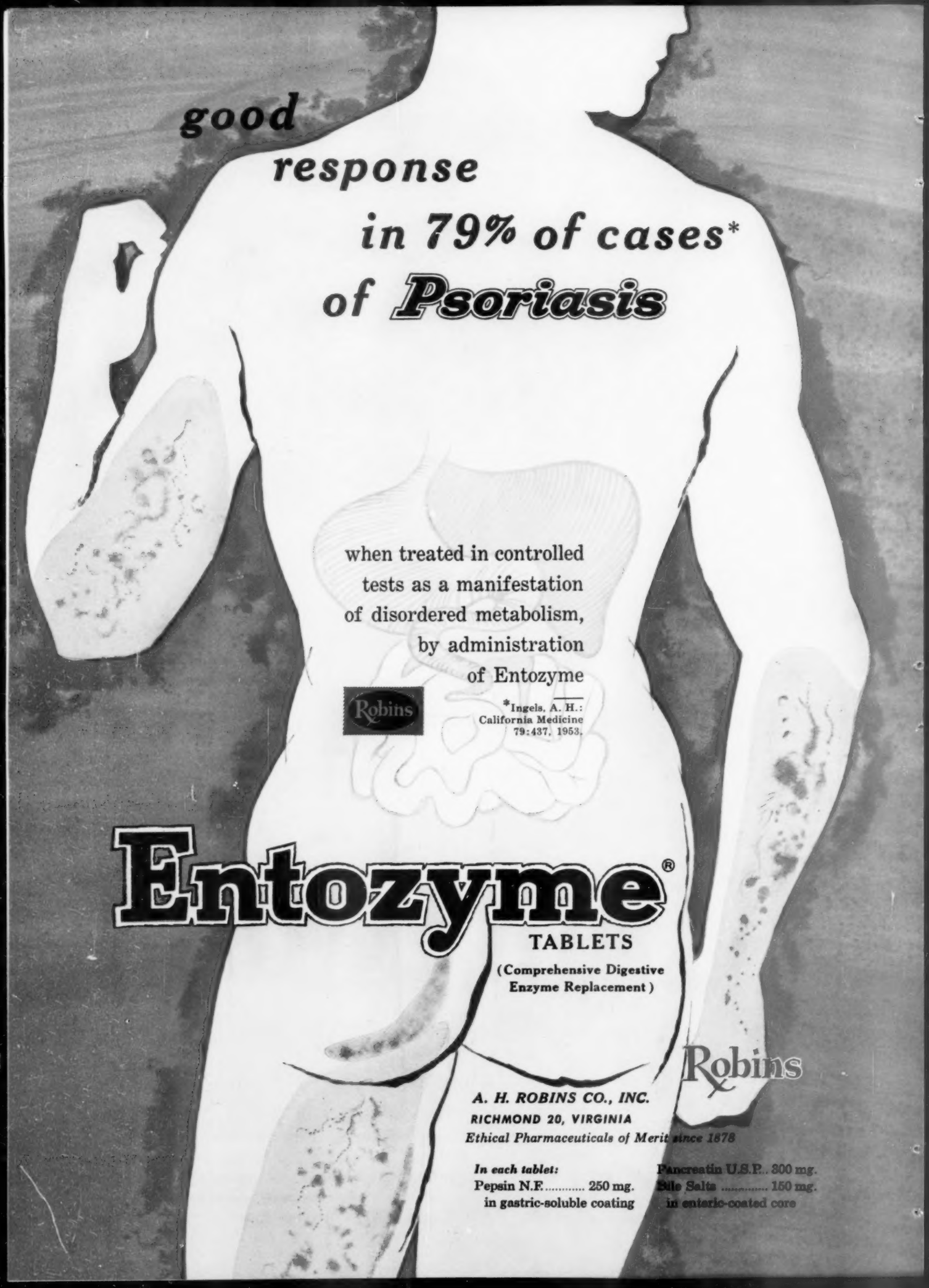
Robins

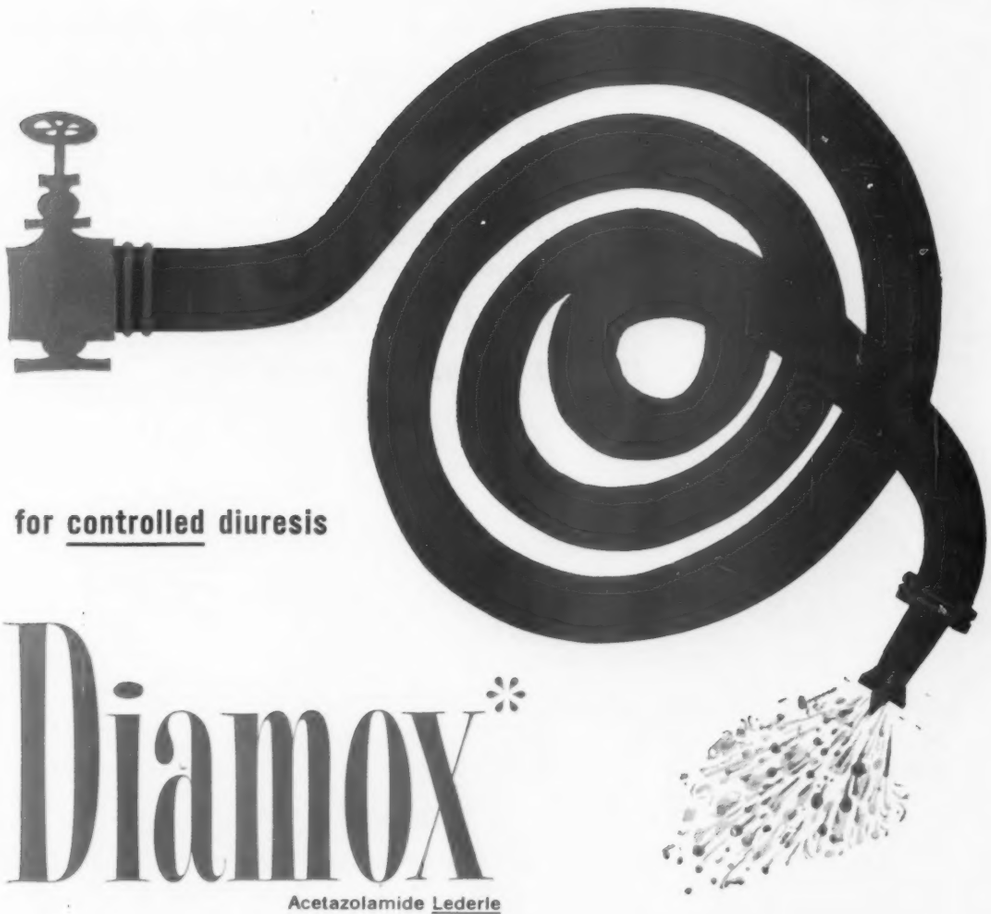
	In each *Tablet*	*Extentab*
Methamphetamine	3.33 mg.	10.0 mg.
Phenobarbital	21.6 mg. (⅓ gr.)	64.8 mg. (1 gr.)

A. H. ROBINS CO., INC., Richmond 20, Virginia
Ethical Pharmaceuticals of Merit since 1878

*an effective psycho-normalizer,
to curb the emotionally spurred appetite*

Methamphetamine for central nervous stimulation (more potent than amphetamine) • with phenobarbital control, in optimal ratio • as plain Tablets — or as Extentabs®, that work all-day on a single dose


good
response
in 79% of cases*
of Psoriasis
when treated in controlled tests as a manifestation of disordered metabolism, by administration of Entozyme
Robins
*Ingels, A. H.: California Medicine 79:437, 1953.
Entozyme®
TABLETS
(Comprehensive Digestive Enzyme Replacement)
Robins
A. H. ROBINS CO., INC.
RICHMOND 20, VIRGINIA
Ethical Pharmaceuticals of Merit since 1878
In each tablet:
Pepsin N.F..... 250 mg.
in gastric-soluble coating
Pancreatin U.S.P.. 300 mg.
Bile Salts ..... 150 mg.
in enteric-coated core



for controlled diuresis

Diamox*

Acetazolamide Lederle

Non-toxic
Non-mercurial
Simple, oral dosage

DIAMOX is an inhibitor of the enzyme carbonic anhydrase; it is not a mercurial or xanthine derivative. It causes prompt, ample diuresis, but its effect lasts only six to twelve hours. As a result, the patient taking DIAMOX in the morning is assured a normal, uninterrupted night's rest.

DIAMOX is not toxic, nor does it accumulate in the body, and patients are slow to develop a tolerance for it. This remarkable drug is therefore well-suited to long-term treatment. Dosage is simple and convenient: one tablet taken orally, each or every other morning.

Indications: cardiac edema, premenstrual tension, acute glaucoma, epilepsy, obesity, and the toxemia and edema of pregnancy.

NOW THE MOST WIDELY PRESCRIBED ORAL DIURETIC!

Tablets of 250 mg. (also in ampuls of 500 mg. for parenteral use when oral ingestion is impractical.)

LEDERLE LABORATORIES DIVISION *AMERICAN CYANAMID COMPANY* PEARL RIVER, N. Y.

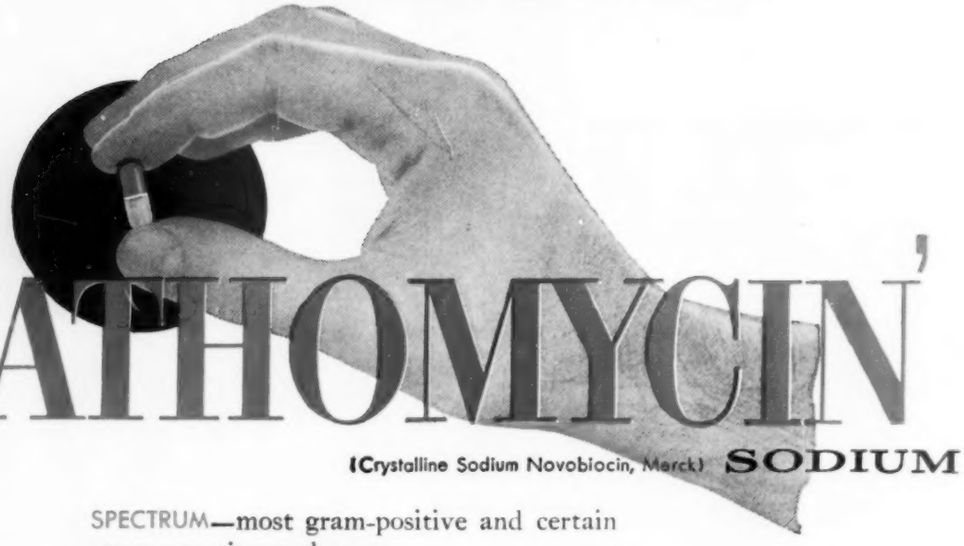
*REG. U. S. PAT. OFF.

NOW AVAILABLE...

a unique new antibiotic of major importance

PROVED EFFECTIVE AGAINST SPECIFIC ORGANISMS
(staphylococci and proteus)

RESISTANT TO ALL OTHER ANTIMICROBIAL AGENTS



'CATHOMYCIN'

(Crystalline Sodium Novobiocin, Merck) **SODIUM**

SPECTRUM—most gram-positive and certain gram-negative pathogens.

ACTION—bactericidal in optimum concentration even to resistant strains.

TOXICITY—generally well tolerated. This is more fully discussed in the package insert.

ABSORPTION—oral administration produces high and easily-maintained blood levels.

INDICATIONS—cellulitis, pyogenic dermatoses, septicemia, bacteremia, pneumonia and enteritis due to *Staphylococcus* and infections involving certain strains of *Proteus vulgaris;* including strains resistant to all other antibiotics.

DOSAGE—four capsules (one gram) initially and then two capsules (500 mg.) twice daily.

SUPPLIED—250 mg. capsules of 'CATHOMYCIN', bottles of 16.

'CATHOMYCIN' *is a trademark of Merck & Co., Inc.*

SHARP & DOHME

Philadelphia 1, Pa.
DIVISION OF MERCK & CO., INC.


6 FLUIDOUNCES
ZIRADRYL®
LOTION
Contains 1% Benadryl Hydrochloride (Diphenhydramine Hydrochloride. P. D. & Co.), 2% Zirconium Oxide (as the Carbonate), Camphor, and 2% Alcohol.
For protection from poison ivy and oak and relief of itching in ivy and oak poisoning.
DIRECTIONS—For protection, apply generously to skin before exposure and after each washing. For relief, cleanse affected area and apply generously three or four times daily. Temporary stinging sensation may follow application. Discontinue use if stinging persists. Easily removed with water.
WARNING—Should not be applied to extensive, or raw, or oozing areas or for a prolonged time except as directed by a physician.
SHAKE WELL BEFORE USING
FOR EXTERNAL USE ONLY
Stock 22-224-39
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PARKE, DAVIS & COMPANY
DETROIT, MICHIGAN, U.S.A.

antihistaminic benefits of Benadryl

neutralizing action of zirconium

ZIRADRYL® LOTION

Benadryl® Hydrochloride with Zirconium

an old favorite in a new form

ZIRADRYL Lotion provides the same recognized clinical advantages as ZIRADRYL Cream. Antihistaminic-antipruritic properties of Benadryl are combined with the urushiol-neutralizing action of zirconium for effective prevention or treatment of ivy or oak poisoning.

protects against rhus dermatitis

if applied before or soon after exposure.

relieves rhus dermatitis

and reduces spreading if applied after dermatitis appears.

ZIRADRYL Lotion is supplied in 6-ounce bottles.
ZIRADRYL Cream is supplied in 1-ounce tubes.

PARKE, DAVIS & COMPANY DETROIT, MICHIGAN

50064

you'd never know he has a peptic ulcer

he's symptom free...

day after day after day...

week after week after week

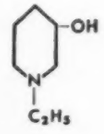
cholinolytic

PIPTAL®

- normacid gastric action
- normalizes G.I. tonus and motility
- prolongs remissions, curbs recurrences
- virtually free from "anticholinergic" side effects

One tablet t.i.d. before meals and 1 or 2 tablets at bedtime. PIPTAL is the *only* brand of N-ethyl-3-piperidyl-benzilate methobromide.

LAKESIDE



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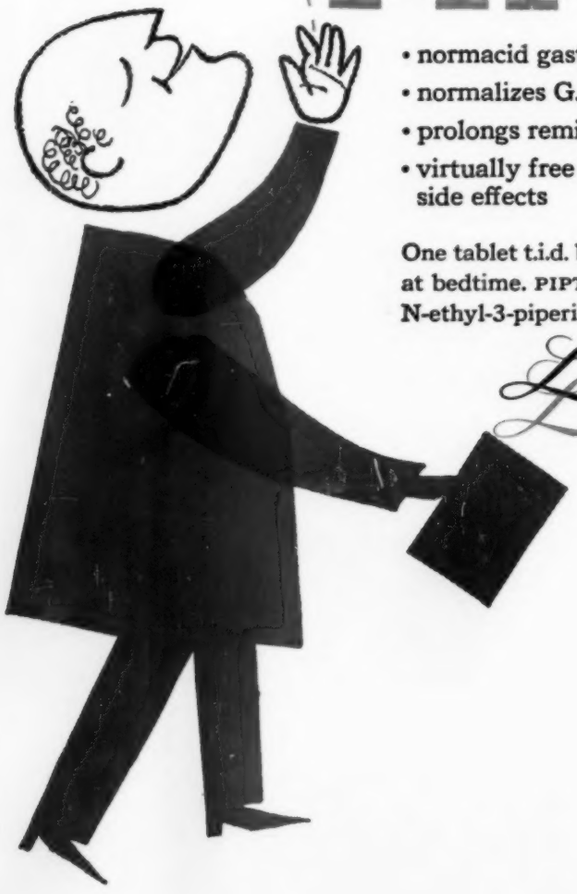

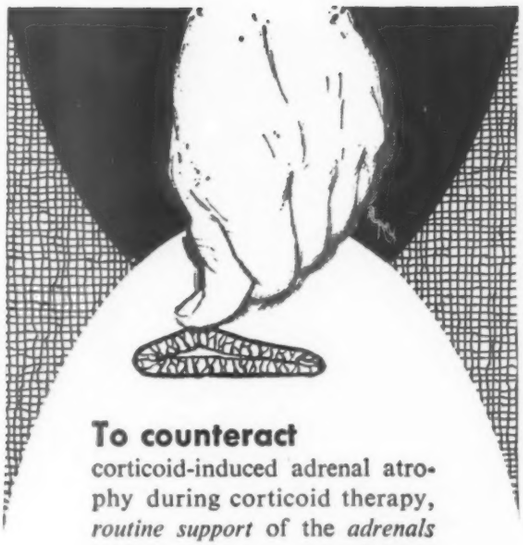

To counteract
corticoid-induced adrenal atrophy during corticoid therapy, *routine support* of the *adrenals with ACTH is recommended.*

THIS IS THE PROTECTIVE DOSAGE RECOMMENDATION FOR COMBINED CORTICOID-ACTH THERAPY

- When using *prednisone* or *prednisolone:* for every 100 mg. given, inject approximately 100 to 120 units of HP* ACTHAR *Gel.*
- When using *hydrocortisone:* for every 200 to 300 mg. given, inject approximately 100 units of HP* ACTHAR *Gel.*
- When using *cortisone:* for every 400 mg. given, inject approximately 100 units of HP*ACTHAR *Gel.*

Discontinue administration of corticoids on the day of the HP*ACTHAR *Gel* injection.

HP*ACTHAR® *Gel*
(IN GELATIN)

The Armour Laboratories brand of purified adrenocorticotropic hormone—corticotropin (ACTH)

*Highly Purified

Unsurpassed in Safety and Efficacy
More than 42,000,000 doses of ACTH have been given

THE ARMOUR LABORATORIES
A DIVISION OF ARMOUR AND COMPANY
KANKAKEE, ILLINOIS

High solubility of "Thiosulfil" insures prompt bacteriostatic concentrations at site of urinary tract infections

direct / effective

"THIOSULFIL"®
Brand of sulfamethizole

AYERST LABORATORIES
New York, N.Y. • Montreal, Canada

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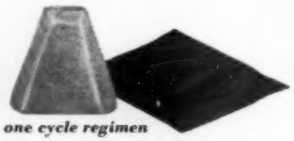


one cycle regimen

Vaginal trichomoniasis: lasting cure for 93.8%

Within 72 hours, local irritation no longer troubled this patient. Relief resulted from thorough powder insufflation by her doctor and her use of suppositories at home.

- after clinical study of 48 active cases, Schwartz reported 93.8% were symptom-free in 3 days; 97.9% showed no motile trichomonads on smear in 7 days; 93.8% had no recurrence 1 to 3 months after treatment through one menstrual cycle*
- advantages: contains a specific, trichomonacidal nitrofuran. Kills many secondary invaders but permits Döderlein's bacillus to exist. Effective in blood, pus and vaginal debris
- office treatment: insufflate TRICOFURON Vaginal Powder twice the first week and once a week thereafter
- home treatment: first week—the patient inserts one TRICOFURON Vaginal Suppository each morning and one each night at bedtime. Thereafter: one a day—a second if needed—to maintain trichomonacidal action

TRICOFURON T. M.

EATON LABORATORIES
Norwich New York

NITROFURANS
a *new* class of antimicrobials
neither antibiotics nor sulfonamides

VAGINAL SUPPOSITORIES AND POWDER

Suppositories: 0.25% Furoxone® (brand of furazolidone) in a water-miscible base of Carbowax and 20 dendro palmitic acid. Sealed in green foil, box of 12.

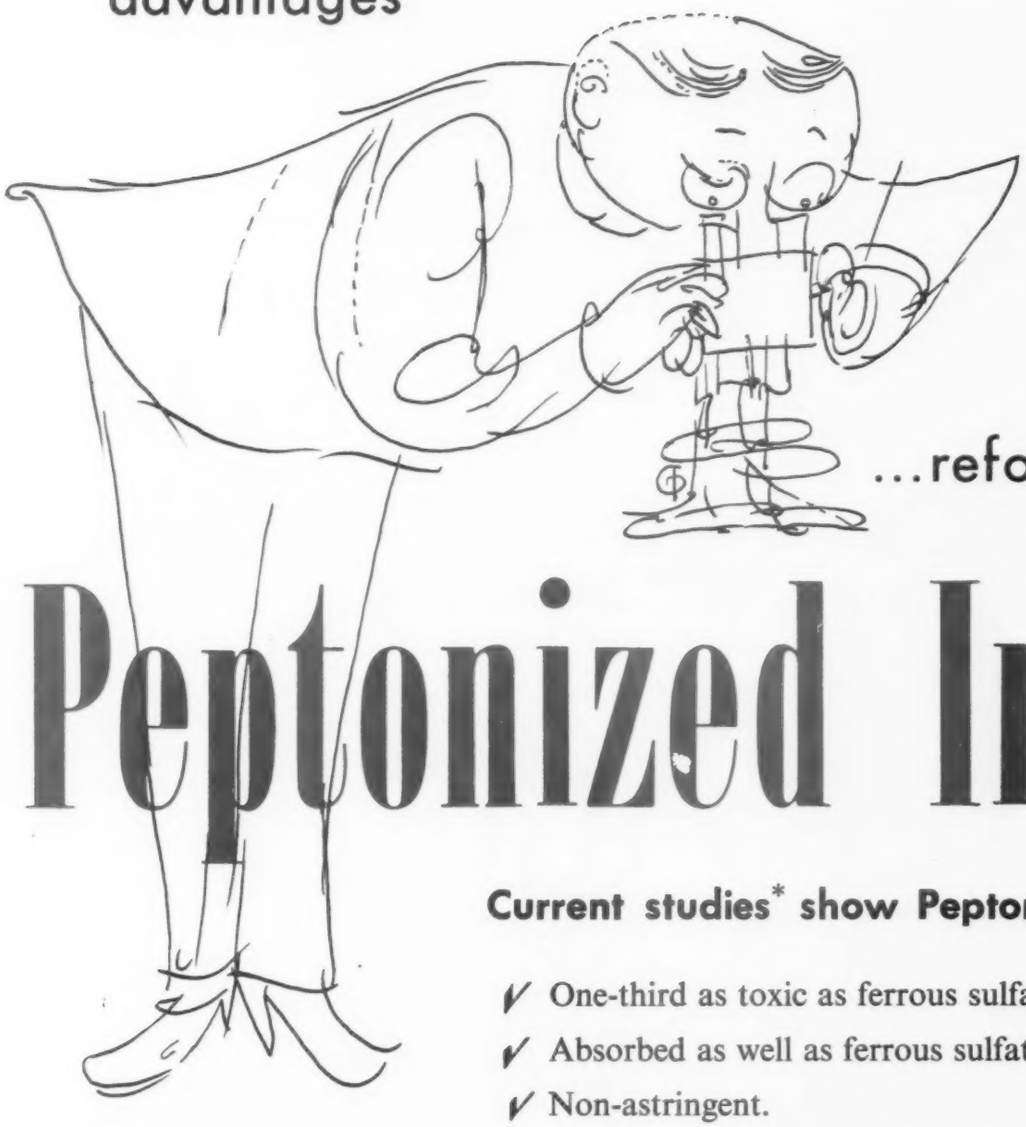
Powder: 0.1% Furoxone in an acidic powder base of lactose, dextrose, citric acid and a silicate. Bottle of 30 Gm.

*Schwartz, J.: Obst. Gyn. N. Y. 7:312, 1956.

for assured

therapeutic

advantages



...refocus on...

Peptonized Iron

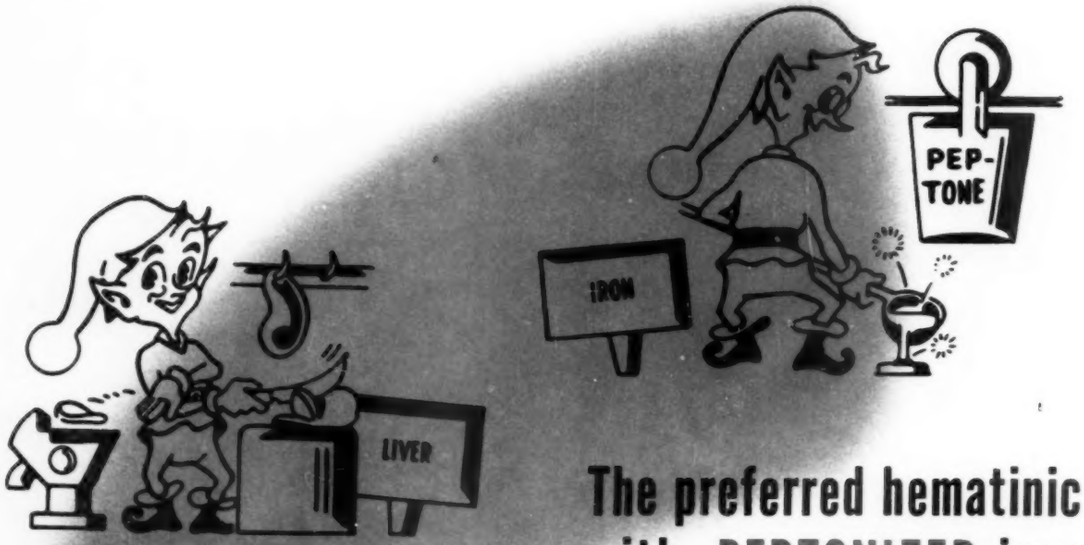
Current studies* show Peptonized Iron—

- ✓ One-third as toxic as ferrous sulfate.
- ✓ Absorbed as well as ferrous sulfate.
- ✓ Non-astringent.
- ✓ Free from tendencies to disturb digestion. (*One-tenth as irritating to the gastric mucosa as ferrous sulfate.*)
- ✓ More effective in iron-deficient anemias.

LIVITAMIN® with Peptonized Iron

*Keith, J. H.: Utilization and Toxicity of Peptonized Iron and Ferrous Sulfate, Read before the American Association for the Advancement of Science, Zoological Section, Atlanta, Georgia, December, 1955.

THE S. E. MASSENGILL COMPANY Bristol, Tennessee • New York • Kansas City • San Francisco



The preferred hematinic with PEPTONIZED iron

LIVITAMIN®

Peptonized iron is virtually predigested. It is absorbed as well as ferrous sulfate, and is one-tenth as irritating to the gastric mucosa. Anemias refractory to other forms of iron will often respond promptly to Livitamin therapy.

The Livitamin formula, containing the B complex, provides integrated therapy to correct the blood picture, and to improve appetite and digestion.

Each fluidounce contains:

Iron peptonized (Equiv. in elemental iron to 71 mg.)	420 mg.
Manganese citrate, soluble	158 mg.
Thiamine hydrochloride	10 mg.
Riboflavin	10 mg.
Vitamin B_{12} (crystalline)	20 mcg.
Niacinamide	50 mg.
Pyridoxine hydrochloride	1 mg.
Pantothenic acid	5 mg.
Liver fraction 1	2 Gm.
Rice bran extract	1 Gm.
Inositol	30 mg.
Choline	60 mg.

THE S. E. MASSENGILL COMPANY

Bristol, Tennessee

New York Kansas City San Francisco

NOW AVAILABLE....

a new unique antibiotic

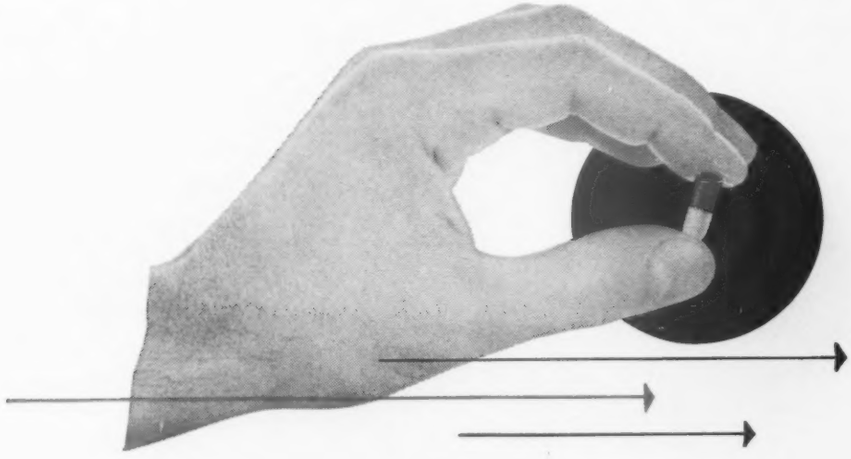
PROVED EFFECTIVE

AGAINST SPECIFIC

ORGANISMS (*staphylococci and proteus*)

RESISTANT TO ALL OTHER

ANTIMICROBIAL AGENTS



to overcome specific infections that do not respond to any other antibiotics.[1,2,3]...

New...

TODAY's resistant pathogens are the tough survivors of a dozen widely used antibiotics. Certain organisms, notably *Staphylococcus aureus*[4] and susceptible strains of *Proteus vulgaris* produce infections which have been resistant to *all* clinically useful antibiotics.

To augment your armamentarium against these resistant infections, 'CATHOMYCIN' (Novobiocin, Merck), derived from an organism recently discovered and isolated in the Merck Sharp & Dohme Research Laboratories[1], is now available.

SPECTRUM—'CATHOMYCIN' [1,2,3,5,6] has also been shown to be active against other organisms including—*D. pneumoniae, N. intracellularis, S. pyogenes, S. viridans and H. pertussis*, but clinical evidence must be further evaluated before 'CATHOMYCIN' can be recommended for these pathogens.

ACTION—'CATHOMYCIN' in optimum concentration is bactericidal. Cross-resistance with other antibiotics has not been observed.[7]

TOLERANCE—'CATHOMYCIN' is generally well tolerated by patients. [5,6,8,9,10,11]

'CATHOMYCIN'

(Crystalline Sodium Novobiocin, Merck) **SODIUM**

ABSORPTION—'CATHOMYCIN' is readily absorbed [5,6,9] and oral dosage produces significant blood and tissue levels which persist for at least 12 hours.[7]

INDICATIONS: Clinically 'CATHOMYCIN' has proved effective for cellulitis, carbuncles, skin abscesses, wounds, felons, paronychiae, varicose ulcer, pyogenic dermatoses, septicemia, bacteremia, pneumonia and enteritis due to *Staphylococcus* and infections caused by susceptible strains of *Proteus vulgaris*.[6,7,8,9,10,11,12,13,14] Also, it is of particular value as an adjunct in surgery since staphylococcic infections seem prone to complicate post-operative courses.

SUPPLIED: 'CATHOMYCIN' Sodium (Crystalline Sodium Novobiocin, Merck) in capsules of 250 mg., bottles of 16.

'CATHOMYCIN' *is a trademark of Merck & Co., Inc.*

REFERENCES:

1. Wallick, H., Harris, D.A., Reagan, M.A., Ruger, M., and Woodruff, H.B., *Antibiotics Annual*, 1955-1956, New York, Medical Encyclopedia, Inc., 1956, pg. 909.
2. Frost, B.M., Valiant, M.E., McClelland, L., Solotorovsky, M., and Cuckler, A.C., *Antibiotics Annual*, 1955-1956, pg. 918.
3. Verwey, W.F., Miller, A.K., and West, M.K., *Antibiotics Annual*, 1955-1956, pg. 924.
4. Kempe, C.H., *Calif. Med.*, **84**:242, April 1956.
5. Simon, H.J., McCune, R.M., Dineen, P.A.P., Rogers, D.E., *Antib. Med.*, **2**:205, April 1956.
6. Lubash, G., Van Der Meulen, J., Berntsen, C., Jr., Tompsett, R., *Antib. Med.*, **2**:233, April 1956.
7. Lin, K.-E., Coriell, L.L., *Antib. Med.*, **2**:268, April 1956.
8. Limson, B.M., Romansky, N.J., *Antib. Med.*, **2**:277, April 1956.
9. Morton, R.F., Prigot, A., Maynard, A. de L., *Antib. Med.*, **2**:282, April 1956.
10. Nichols, R.L., Finland, M., *Antib. Med.*, **2**:241, April 1956.
11. Mullins, J.F., Wilson, C.J., *Antib. Med.*, **2**:201, April 1956.
12. David, N.A., Burgner, P.R., *Antib. Med.*, **2**:219, April 1956.
13. Marton, W.J., Heilman, F.R., Nichols, D.R., Wellman, W.E., and Geraci, J.E., *Antib. Med.*, **2**:258, April 1956.
14. Milberg, M.B., Schwartz, R.D., Silverstein, J.N., *Antib. Med.*, **2**:286, April 1956.

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Philadelphia 1, Pa.
DIVISION OF MERCK & CO., INC.

forecast:

picnics and pollen

time for

Tyzine®

brand of tetrahydrozoline hydrochloride

for relief of allergic nasal congestion in minutes for hours

When hay fever and other seasonal allergies have a field day, remember the "superior"[1-3] decongestive properties of TYZINE . . . effective immediately and lasting up to 6 hours or longer after a single application . . . odorless, tasteless . . . free of sting, burn, irritation and rebound congestion.

Supplied:

TYZINE Nasal Solution, 1-oz. dropper bottles, 0.1%. Nasal Spray, 15 cc., in plastic bottles, 0.1%. Pediatric Nasal Drops, 1/2-oz. bottles, 0.05%, with calibrated dropper for precise dosage.

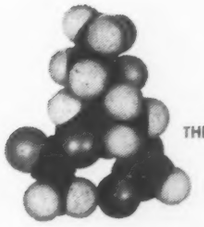
Note: As with certain other widely used nasal decongestants, overdosage may cause drowsiness in infants and children. Although no effect on blood pressure has been reported, it is recommended that caution be observed in treating hypertensive or hyperthyroid patients.

1. Pace, W. G.: Mil. Med. 118:34, 1956.
2. Graves, J. W.: Eye, Ear, Nose & Throat Month. 34:670, 1955.
3. Menger, H. C.: New York J. Med. 55:812, 1955.

Pfizer **PFIZER LABORATORIES**

Division, Chas. Pfizer & Co., Inc.

Brooklyn 6, New York



THE MILTOWN MOLECULE

A tranquilizer well suited for prolonged therapy

NO ORGANIC CONTRAINDICATIONS

reported to date

- well tolerated, non-addictive, essentially non-toxic
- no blood dyscrasias, liver toxicity, Parkinson-like syndrome or nasal stuffiness
- chemically unrelated to chlorpromazine or reserpine
- does not produce significant depression
- orally effective within 30 minutes for a period of 6 hours

Indications: anxiety and tension states, muscle spasm.

Miltown®

the original meprobamate— 2-methyl-2-*n*-propyl-1,3-propanediol dicarbamate—U.S. Patent 2,724,720

SUPPLIED: 400 mg. scored tablets. Usual dose: 1 or 2 tablets t.i.d.

DISCOVERED AND INTRODUCED by Wallace Laboratories, New Brunswick, N. J.
Literature and Samples Available on Request

the 2 favored asthma treatments

First, hold tablet under the tongue 5 minutes for fast sublingual action of aludrine (Isopropyl arterenol).

Then, swallow tablet for 4-hour protection with theophylline-ephedrine-phenobarbital.

Your asthma patients will prefer convenient NEPHENALIN. One tablet as needed (up to 5 a day). Bottles of 20 and 100.
THOS. LEEMING & Co., INC., New York 17, N.Y.

Nephenalin® *(for adults)* **Nephenalin® PEDIATRIC**

When diarrhea follows indiscreet eating, prescribe...

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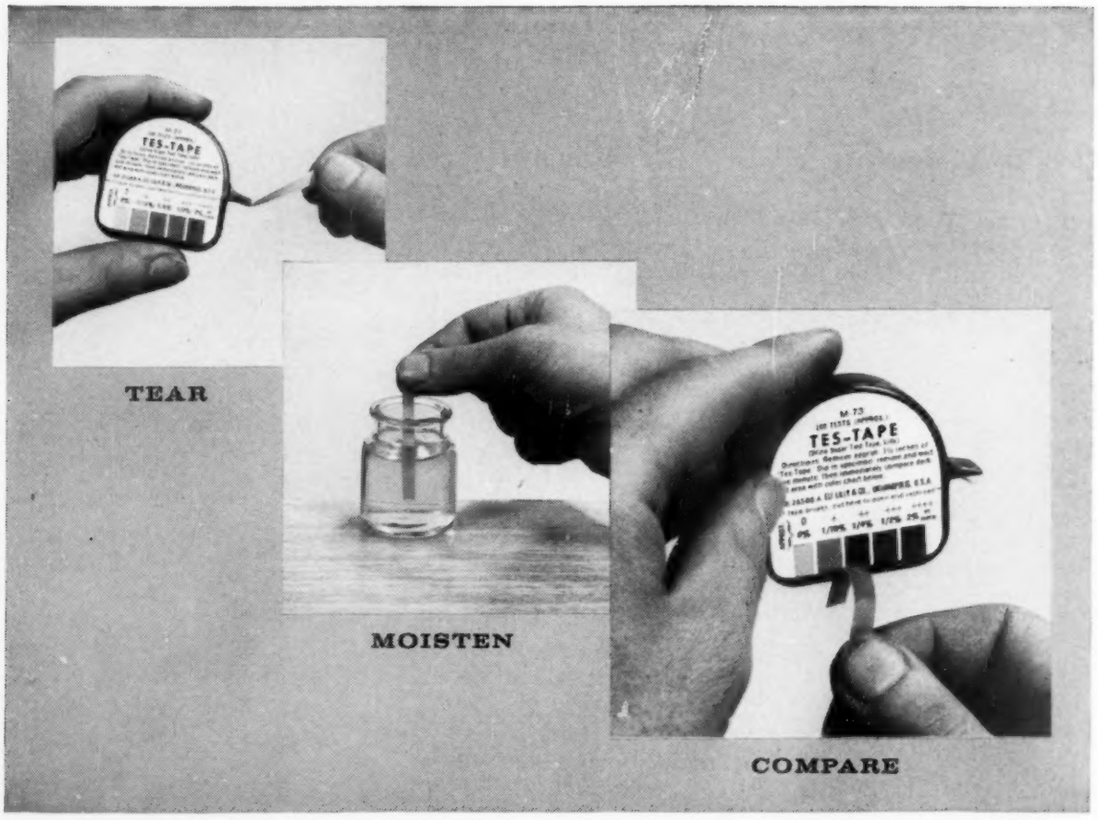

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The American Journal of Medicine

VOL. XXI JULY, 1956 No. 1

Editorial

Ten Years of the "Green Journal"

THIS issue initiates the second decade of publication of The American Journal of Medicine. The occasion is appropriate for an assessment of policy, a review of past accomplishment and an analysis of the present position of the Journal.

When introduced in 1946 the first editorial dealt with the objectives of the new Journal. It was suggested that, in view of the expanding programs of medical research then (as now) being made possible by increasing public and private support, there might be need of an additional medium for publication of sound clinical investigation. The principal purpose of the new Journal would be, however, to further medical education at the postgraduate level by helping to make more widely known the activities particularly of our large medical schools and teaching hospitals. "The teaching opportunities of the medical periodical are very great even though, it must be admitted, often inadequately realized." The new Journal was to attempt to exploit these teaching opportunities more fully by including in its text not only such usual categories as original clinical investigation, case reports and editorials but also, as regular features, reviews and symposia, clinicopathologic conferences, conferences on mechanisms of disease and conferences on therapy. All this was to be maintained at a high level of professional competence and the whole was to appear in esthetically pleasing format with distinguished typography.

It must be confessed that this large enterprise was undertaken with some anxiety. There was then, as now, no dearth of medical journals and there was no assurance that another, however well intended, could survive. Moreover, The American Journal of Medicine was not the official organ of any established medical organization and did not enjoy the moral and financial backing afforded by a large society membership. There was no way of knowing whether publication of the abstrusities of modern medical investigation would prove of sufficient interest to the busy practitioner and student to enlist their support.

It is therefore a matter of some satisfaction to report that the events of the past ten years have borne out the presumptions that led to the founding of the "Green Journal," as it soon came to be known. Almost from the start there was a sufficiency of deserving manuscripts and before long far more than could possibly be accommodated, even in greatly expanded issues; this embarrassment of riches would appear to establish that there really was a need for some appropriate medium for publication. Almost from the start, also, the Journal was accepted as a vehicle for teaching, both by those who would teach and by those who would be taught. As a recent survey disclosed, an astonishingly broad cross-section of the profession makes regular use of The American Journal of Medicine for serious study of current developments in medicine—the internist, the general practitioner, the medical student, intern and resident, the young physician preparing for one or another examination, the most diverse specialists. The paid circulation has grown steadily and has for some time been the largest of the "independent" medical journals (i.e., those not serving as organs of medical societies).

Such generous support, both in this country and abroad, would seem to vindicate the policy of the Journal, to strive to maintain the highest

possible standards of uncompromising scholarship, and this we propose to do. But perhaps the most gratifying aspect of such wide acceptance is this demonstration that there are so many serious students of all ages, climes and special interests who are prepared to interrupt their busy careers to struggle with the complexities of modern clinical investigation. Surely, this bodes well for the future of medicine!

The American Journal of Medicine owes its acceptance to the efforts of many. Its Editorial Board has always been composed of distinguished physicians, seasoned veterans in teaching and investigation. Special thanks are due to those who have completed their tenure on the Editorial Board: Francis G. Blake, Herrman L. Blumgart, Harry Gold, George H. Houck, Chester S. Keefer, T. Grier Miller, Walter W. Palmer (whose encouragement and aid in the early days of the Journal deserves added acknowledgment), Oswald H. Robertson, Ephraim Shorr, Eugene A. Stead, William S. Tillett, Joseph T. Wearn, Russell M. Wilder, Maxwell M. Wintrobe, W. Barry Wood and John B. Youmans.

The quality of the Journal can be no higher than the quality of the papers appearing in its pages, hence a great debt of gratitude is owing to the many authors who have made known significant additions to medical knowledge through this medium. Perusal of the issues that have appeared over the past ten years reveals a gratifying proportion of contributions that have stood the test of time. Special thanks are due the editors of the Columbia Combined Staff Clinics, the Cornell Conferences on Therapy, the Harvard Conferences on Psychosomatic Problems, and the Washington University Clinicopathologic Conferences, which appear regularly in the Journal. We are further indebted to the many invited contributors to symposia, seminars and reviews who have given unstintingly of their time and effort to further the teaching aims of the Journal.

Finally, there are our many faithful subscribers and advertisers whose support has made this undertaking possible. The Editorial Board and the publishers will endeavor to maintain the high aims and standards of the Journal and thus merit their continued interest. We set our forward course with confidence and determination!

THE EDITOR

Clinical Studies

The Problem of Chronic Liver Disease in Young Women*

A. G. Bearn, M.D., H. G. Kunkel, M.D. *and* R. J. Slater, M.D.
New York, New York

In 1951 two short reports from this laboratory[1,2] called attention to a group of patients suffering from a rather unusual form of cirrhosis of the liver. These patients, predominantly young women, were considered together because they exhibited certain clinical and biochemical characteristics which were not ordinarily seen in cases of either classic post-hepatitis cirrhosis or Laennec's cirrhosis. Subsequent experience at this hospital during the past five years has revealed that the majority of young adults with evidence of severe hepatic cirrhosis and in whom no alcoholic or nutritional etiology was apparent have also been women. Some of these patients gave a history suggestive of acute hepatitis, a few were shown to be suffering from Wilson's disease, and occasionally other rare but recognizable disorders have been encountered. In the majority of cases, however, the etiologic agent responsible for the hepatic cirrhosis has remained obscure.

Occasional cases of hepatic cirrhosis falling into this category have been recognized in the past.[3–9] However, the collection of a large number of cases of hepatic cirrhosis in young women appeared of itself to warrant a reconsideration of some of the problems involved. A total of twenty-six such patients with hepatic cirrhosis have now been studied at the Rockefeller Institute, and a consideration of some of their clinical, pathologic and biochemical features forms the substance of this article.

The patients included in the present report represent all the young adults with severe cirrhosis of the liver observed at the Rockefeller Hospital, with the exception of those cases with clearly discernible etiologic factors. Six patients with cirrhosis after classic well defined acute infectious hepatitis have been excluded. The clinical manifestations and biochemical findings of the cirrhosis which followed acute hepatitis in this group of patients were of the usual type and appeared to differ from those seen in most of the present group of patients. However, seven of the twenty-six cases considered in this report were included because, although a previous attack of atypical acute hepatitis appeared possible, they shared with other members of the group certain unusual features not commonly encountered in classic post-hepatitis cirrhosis, for example, arthritis and amenorrhea. Further medical inquiry into the previous medical history of the remaining nineteen cases was singularly unproductive. The onset of the illness was usually insidious and was unheralded by any gastrointestinal disturbances commonly seen in the early stages of acute hepatitis. It should be emphasized that the decision whether to include certain persons within the main group proved at times extremely difficult; this difficulty was further enhanced by the inherent uncertainties in the diagnosis of acute viral hepatitis. Since asymptomatic forms of the disease may occur[10,11] it cannot be stated categorically that none of the nineteen patients who failed to give a history of acute infectious hepatitis had not, in fact, contracted the disease at some time in the past. Certainly some of the unusual clinical manifestations noted in this group of patients have been observed in patients giving a classic history of acute infectious hepatitis.

CLINICAL FEATURES

Although the patients to be described exhibited, in varying degrees, many of the signs and symptoms common to chronic liver disease due to a variety of causes, only those symptoms and signs which differentiate this group of pa-

* From the Rockefeller Institute for Medical Research, New York, New York.

TABLE I

CLINICAL FEATURES OF TWENTY-SIX PATIENTS WITH CIRRHOSIS OF THE LIVER

Case No.	Patients Initials and Hosp. No.	Age Onset	Sex	Earliest Symptoms	Menses	Arthritis	Febrile Episodes	Striae	Liver	Spleen	Varices	Ascites	Antecedent Hepatitis	Antecedent Estrogens	Duration (yr.)
1	D. M. 12489	17	F	Fatigue; jaundice	A	0	0	++	++	+	+++	++	0	+	5†
2	J. G. 12547	12	F	Jaundice	A	++	++	0	+	++	+	0	Possible	0	11†
3	T. St. 12271	9	F	Jaundice	A	++	++	0	+++	++	?	0	0	0	4†
4	T. F. 12599	3	F	Anorexia; abdominal enlargement	A	0	0	0	+++	++++	0	++++	0	0	11
5	C. P. 13450	9	F	Fatigue; jaundice	A	0	0	0	+	++	0	0	0	0	3
6	C. G. 12454	16	F	Obesity; amenorrhea	A	0	0	+++	+	++	+++	++	0	0	4†
7	D. P. 12609	15	F	Fatigue	A	0	0	++	0	+	0	+	0	0	3‡
8	M. S. 12441	13	F	Fever; epistaxis	A	0	0	0	+	+++	0	0	0	+	7
9	E. C. 12252	10	F	Fatigue; anorexia	A	0	0	+	0	+	+++	0	0	0	8†
10	L. B. 12243	33	F	Arthritis; jaundice	A	+++	++	0	++	+++	+++	++	0	0	9†
11	R. M. 12194	16	F	Amenorrhea; jaundice	A	0	0	0	+	++	++	+	0	0	3
12	J. A. 12516	16	F	Amenorrhea; obesity	A	0	++	+	+	++	0	++	0	0	3†
13	F. W. 12478	27	F	Arthritis; amenorrhea	A	++	0	0	++	+	++	0	Possible	0	2†
14	J. S. 12240	17	F	Amenorrhea; arthritis	A	++	++	0	+	+	0	0	0	0	9
15	M. S. Bellevue #65113-42	16	F	Bleeding gums; arthritis	Not known	+++	++	0	+	0	No inf.	0	0	0	No info.
16	T. S. 12581	11	F	Bleeding gums; jaundice	A	0	0	0	++	+++	++	+++	0	0	3†
17	D. F. 12231	29	M	Jaundice	Not Appl.	+++	0	0	+	+	0	0	Possible	0	12
18	J. W. 14656	10	M	Fatigue; arthritis	Not Appl.	++	0	0	++	0	0	0	0	0	2
19	I. M. 12761	18	F	Fever; jaundice	I	++	++	0	+	+	+	+	0	+	12†
20	L. N. *	18	F	Bleeding gums; jaundice	A	0	0	0	+	+++	0	0	Possible	0	0
21	L. McC. 15058	15	M	Jaundice	Not Appl.	++	++	0	+	++	+++	0	0	0	3
22	R. A. 12110	13	F	Jaundice	A	0	0	0	+	+++	+++	+	Possible	+	20†
23	J. St. 15231	14	F	Malaise; jaundice	I	0	0	++	+	++	0	0	0	0	1
24	H. P. 12167	19	F	Fever; arthritis	I	+++	+++	0	+++	++	+++	0	0	0	10
25	S. G. 12266	12	F	Malaise; jaundice	A	0	++	0	+++	+	0	+	Possible	0	7†
26	E. M. 13759	13	F	Jaundice; vomiting	A	0	0	0	+++	++	0	++++	Possible	0	3

A = Amenorrhea
I = Irregular menstruation
* = Patient under care of Dr. D. H. Labby, Portland, Oregon
† = Died
‡ = Accidental death

tients from the more common types of cirrhosis will be discussed in detail. A summary of the more pertinent clinical findings is given in Table 1.

The predominance of women in this group of cases was very striking; only three of the twenty-six patients (11.5 per cent) were men. There was no convincing racial or ethnic predominance; however, the numbers studied were too small for any dogmatic assertions on these points. The youngest patient in whom symptoms relating to liver disease were noted was a female child aged three; the oldest subject in this series was a woman of thirty-three years. The average age of onset was fifteen years, with twenty of the twenty-six cases (76.9 per cent) first displaying symptoms between the ages of ten and twenty.

Delayed menstruation or amenorrhea prior to or coincident with the onset of symptoms occurred in fifteen of the twenty-three women; in an additional five cases various degrees of amenorrhea developed during the course of the disease. It is particularly noteworthy that two of the patients who had some degree of menstrual irregularity became pregnant, and subsequently each was delivered of a live child. One of these cases has been the subject of a separate report by Slater.[12] Because amenorrhea or delayed menstruation often preceded overt symptoms of liver disease, medical advice was frequently sought on this account. In three instances estrogens were known to have been administered in an effort to induce uterine bleeding. Unfortunately, the true incidence of estrogen administration prior to the onset of liver disease is unascertainable since specific inquiry concerning this point was not made in all of the twenty-three female patients. Onset of the disease at or near the time of puberty (between the ages of twelve and sixteen) was noted in fourteen of the twenty-three female patients.

In two of the patients (J. A., C. G.) a rapid increase in weight in the year preceding recognition of the liver disease had led to the administration of thyroid hormone by the attending physician. The start of the illness was typically gradual. Exertional fatigue and lassitude were common early symptoms. The insidious onset of symptomless jaundice was frequently the first indication that the liver was affected by the disease process. More rarely, severe and persistent bleeding of the gums and frequent epistaxis prompted hematologic investigations which in turn led to the suspicion of hepatic disease. Obscure febrile episodes associated with joint pains occurred as early symptoms in a few cases. More commonly arthralgia, when present, developed during the course of the disease. Characteristically, and in marked contrast to the usual cases of Laennec's cirrhosis, the patients were frequently well nourished and indeed in some cases were somewhat overweight. Evidence of severe cirrhosis was usually found at the time of the first examination by the physician and was revealed either by clinical examination or, with more certainty, from a study of the liver function tests.

In addition to the presence of amenorrhea, on rare occasions acne, hirsutism, pigmented striae, obesity and moon facies were early symptoms and were noted before the onset of overt jaundice or the recognition of liver disease (C. G., D. C., J. A., M. S.). These symptoms were somewhat reminiscent of those seen in patients with Cushing's syndrome. In one patient (J. S.) purplish striae were present without any of the other features mentioned. However, in contrast to most cases of Cushing's syndrome, hypertension and osteoporosis were conspicuous by their absence. The possibility was considered that striae, when present, were due to the rapid onset of obesity rather than to hormonal influences. The site of the striae, their color and the fact that they also appeared in those patients who were not overweight rendered this interpretation less likely.

In some instances transient rashes similar to those seen in erythema multiforme were seen early in the course of the disease. In one patient (L. B.) three separate episodes of erythema multiforme occurred during the duration of the illness.

CLINICAL COURSE

The well nourished and relatively healthy appearance of these patients belied the seriousness of their disease. Three patients who clinically appeared to be relatively well but were found on closer examination to be suffering from severe liver disease are illustrated in Figure 1. As the disease progressed the classic signs of hepatic cirrhosis, which in most patients were clearly recognizable early in the disease, became increasingly apparent. Variation in the size of the liver was noted in some patients. The spleen was usually considerably enlarged and was frequently palpable at the earliest recognizable stage of the disease. In some patients spleno-

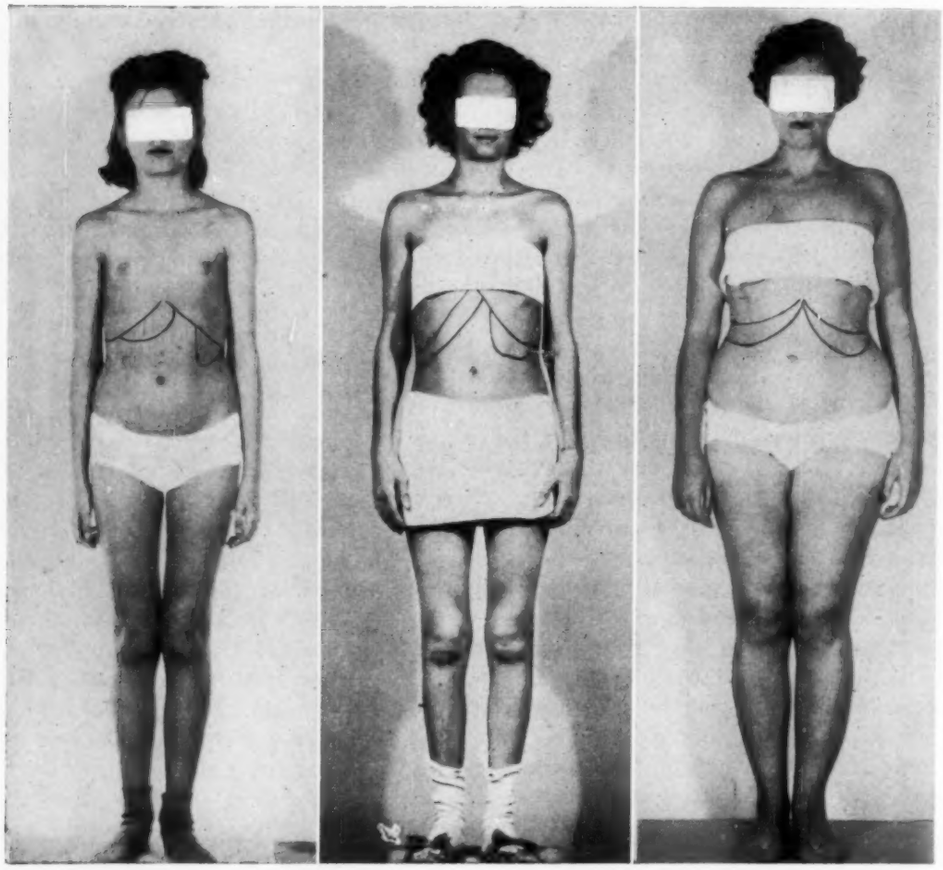

FIG. 1. Three female patients (E. C., J. S., J. St.) with severe cirrhosis of the liver of unknown etiology.

megaly was the most strikingly abnormal clinical finding and occasionally the enlargement of this organ was very great indeed. Variation in the size of the spleen during the course of the disease was a frequent occurrence. The splenic enlargement, although usually symptomless, was sometimes associated with a sensation of dragging discomfort in the left side of the abdomen. Rarely, acute episodes of splenic pain, sometimes coincident with an elevation in temperature, suggested minor degrees of infarction of this organ. Spider angiomas and liver palms developed in the majority of the patients. Clubbing of the fingers was uncommon.

Varices demonstrable radiographically were present in twelve of the twenty-six cases and overt esophageal hemorrhage occurred in eleven. In three patients a portacaval shunt was successfully carried out and in one a splenorenal shunt was performed. Clinical ascites, in sharp contrast to many patients with Laennec's cirrhosis, was a relatively uncommon finding in the early stages of the disease. During the final episode of hepatic decompensation clinical evidence of ascites developed in most patients; in only five cases, however, was the accumulation of ascites a serious clinical problem.

In ten patients obscure febrile episodes sometimes associated with respiratory or cardiac symptoms occurred at some time during the course of the disease. Numerous blood cultures were performed in an attempt to isolate a bacterium, but in no case was a positive blood culture obtained. In one patient (H. P.) there were recurrent febrile episodes, with a rectal temperature as high as 104°F. In addition, precordial pain, gallop rhythm and shortness of breath were associated with increased cardiac size and occurrence of a small pleural effusion. Electrocardiographic examination in this patient revealed S-T depression in several leads with inversion of the T waves in the precordial leads. During the acute episodes of the disease the patient appeared gravely ill but with treatment there was a return

FIG. 2. Roentgenogram of ankle joints of patient L. B. showing diminution of the joint spaces and evidence of arthritis.

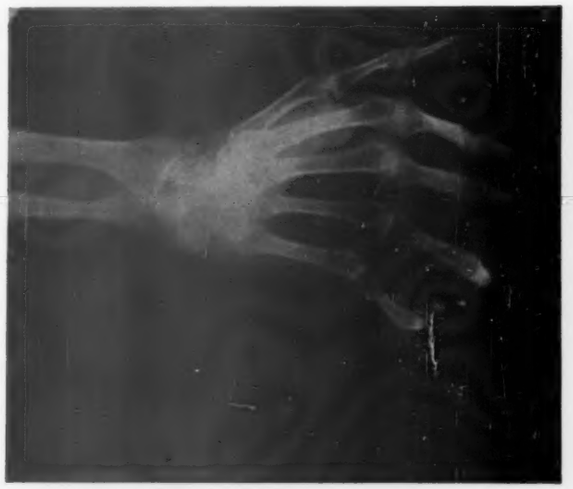

FIG. 3. Roentgenogram showing considerable deformity and arthritis of the interphalangeal joints of patient L. McC.

within one to two weeks to the clinical condition present before the exacerbation. On one occasion, at the height of such an episode, a few typical L.E. cells were seen in the blood.* Although a search for L.E. cells was undertaken in a number of other patients none were found.

A surprising number of patients (eleven of twenty-six, or 42 per cent) complained of joint pains of varying severity. These symptoms usually occurred early in the course of the illness and in some instances were accompanied by an acute non-bacterial febrile episode associated with a temporary exacerbation of the liver disease. In three cases (H. P., L. B., L. McC.) chronic changes in the joint ensued which resembled those seen in typical chronic rheumatoid arthritis. (Figs. 2 and 3.) The joints most commonly affected were the ankles and wrists (nine and seven cases, respectively). The most common complaint encountered was stiffness, sometimes amounting to pain, of the affected joints. Although swelling of the periarticular tissues was a frequent accompaniment of the early stages, redness was somewhat uncommon. In two patients (J. S., H. P.) rheumatic nodules were present. In two cases fluid was aspirated from the knee joint (L. B., M. S.) and in one case fluid was removed from the elbow (M. S.). The fluid aspirated was essentially normal. Bacteriologic examination of the aspirated fluid was negative in two cases. In one case (M. S.) an organism resembling Brucella abortus was cultured, which later was considered to be a laboratory contaminant. Although permanent and disabling sequelae were extremely rare, in one case (L. B.) fixation of the ankle joint resulted in difficulty in walking, and in another (L. McC.) dislocation of the interphalangeal joints prevented the execution of fine movements.

Death from the disease within ten years of onset was the rule but many patients led active and useful lives for a longer period. A few patients improved considerably and one patient (D. F.) made a remarkable clinical recovery. Twelve years after his first admission to hospital, and despite the persistence of abnormal liver function tests, he is actively engaged in psychiatric practice.

Death was predominantly due to either esophageal hemorrhage or progressive hepatic coma. In most instances death resulted from a combination of factors and the terminal episode was frequently precipitated by an intercurrent infection. Thus far twelve of twenty-five patients have died as a direct result of the disease process. The average duration of the disease in those who have already died was about seven years (range three to twenty). The mean duration of the dis-

* We are indebted to Dr. Paul Klemperer, Mount Sinai Hospital, New York, for this information.

ease in those still living (November 1, 1955) is five and a half years (range one to twelve).

LABORATORY INVESTIGATIONS

An earlier report[1] emphasized the unusually marked serum protein changes occurring in this

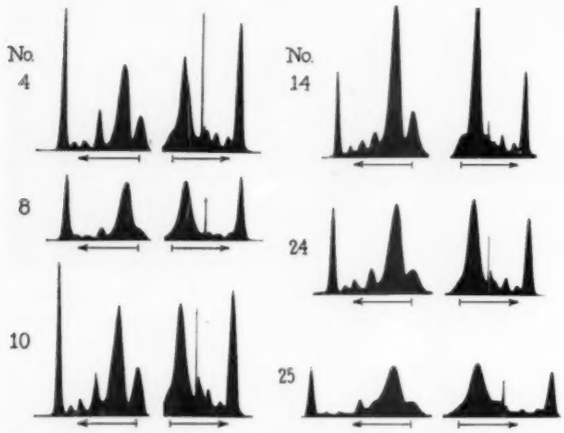

FIG. 4. Electrophoretic patterns of the serum of six patients with cirrhosis of the liver and hyperproteinemia showing considerable elevation of gamma globulin.

group of patients compared with those found in Laennec's cirrhosis. Further experience has, in general, borne out these observations. The chief biochemical results obtained in twenty-six patients are illustrated in Table II. Details of the biochemical methods employed during the course of the investigation have been reported in previous papers from this laboratory.[13,14] In the early stages of the disease the total serum protein concentration was usually but by no means invariably elevated considerably. This elevation was due in large part to a greatly increased gamma globulin component of serum, with a relatively normal level of serum albumin. The mean level of serum total protein in twenty-six cases studied was 9.3 gm. per cent (range 6.3 gm. per cent to 13.1 gm. per cent). No less than ten of twenty-six patients (38.4 per cent) had a serum total protein concentration greater than 10 gm. per cent. The serum gamma globulin was elevated in all cases; the highest figure recorded was 9.4 gm. per cent (E. N.). Electrophoretic separation of the sera from eleven of these patients confirmed the hypergammaglobulinemia. (Fig. 4.) Separation of the sera by the method of zone electrophoresis using various supporting media gave essentially similar results. The turbidity and flocculation tests in this group of patients were remarkable only insofar as they reflected to varying degrees the increase in gamma globulin.[15]

The elevation of the serum proteins so characteristic of the early stages of the disease diminished with progressive deterioration of liver function. A slow but steady decline of the gamma globulin was accompanied in the later stages of the disorder by a decrease in the serum

TABLE II

BIOCHEMICAL FEATURES OF TWENTY-SIX PATIENTS WITH CIRRHOSIS OF THE LIVER

Case No.	Patient's Initials and Hosp. No.	Serum Total Protein* (gm. %)	Serum Albumin (gm. %)	Serum Globulin (gm. %)	Serum Bilirubin (mg. %)	BSP Retention (%)
1	D. M.	7.6	3.3	5.6	4.3	35
	12489	7.8	2.1	4.5	3.3	36
2	J. G.	9.7	1.5	5.6	5.7	32
	12547	6.3	3.6	3.3	2.8	..
3	T. St.	10.8	2.7	8.2	10.0	26
	12271	10.5	2.0	8.6	8.6	40
4	T. F.	8.5	2.7	4.7	2.9	24
	12599	6.9	2.3	4.3	....	31
5	C. P.	10.2	3.1	6.1	4.6	41
	13450	10.2	3.0	6.0	10.0	..
6	C. G.	8.2	2.8	5.1	13.8	34
	12454	8.0	3.0	4.6	11.9	..
7	D. P.	6.4	2.4	4.0	5.5	14
	12609	6.2	3.1	3.1	7.3	43
8	M. S.	10.6	2.5	5.6	8.0	34
	12441	10.2	...	5.2	2.9	..
9	E. C.	9.6	2.9	6.6	2.0	20
	12252	10.6	4.2	6.3	1.8	14
10	L. B.	8.3	3.5	4.8	2.0	6
	12243	9.1	...	6.0	4.2	40
11	R. M.	6.8	2.3	4.5	5.1	42
	12194	6.5	3.4	3.1	1.8	31
12	J. A.	7.3	1.6	5.7	1.4	40
	12516	6.8	1.5	5.3	....	..
13	F. W.	8.8	3.8	5.0	7.0	29
	12478	7.3	3.5	3.8	8.4	..
14	J. S.	11.4	2.2	9.2	12.3	24
	12240	11.0	3.0	8.0	8.7	..
15	M. S.	10.4	3.0	7.5	....	..
	Bellevue	9.8	2.5	7.3	....	..
16	T. S.	8.7	4.2	4.5	1.8	31
	12581	8.7	4.4	4.3	1.3	..
17	D. F.	9.3	3.3	6.0	1.7	20
	12231	8.5	3.0	5.5	5.6	..
18	J. W.	9.6	4.5	4.3	0.4	2
	14636	8.7	4.9	4.3	0.4	..
19	I. M.	8.2	3.6	4.3	10.6	25
	12761	8.0	4.4	3.5	1.2	..
20	L. N.	12.0	4.1	7.9	6.0	..
		12.5	3.2	9.3	....	..
21	L. McC.	9.4	1.3	6.1	13.2	28
	15058	7.8	2.1	5.6	5.0	..
22	R. A.	8.7	3.6	5.1	1.3	30
	12110	7.6	4.3	3.3	....	..
23	J. S.	6.3	3.8	3.2	1.6	44
	15231	6.6	4.0	4.2	4.2	..
24	H. P.	13.1	3.7	9.4	2.7	20
	12167	10.3	3.3	7.0	2.1	..
25	S. G.	11.5	3.1	6.8	1.9	17
	12266	12.0	1.3	7.0	2.0	27
26	E. M.	10.4	1.2	7.1	3.6	32
	13759	10.4	1.3	6.8	2.0	..

*Some total protein values do not correspond in time with albumin and globulin determinations cited.

albumin concentration. Prior to death the protein disturbances differed little if at all from those seen in Laennec's cirrhosis. A prompt fall in the serum total protein concentration frequently followed severe hemorrhage and even though the patient survived this the serum total protein rarely returned to the pre-hemorrhage value.

As in many patients with classic Laennec's cirrhosis, jaundice was a common clinical finding. Serum bilirubin concentrations of 3.0 to 5.0 mg. per cent were frequent, and unaccompanied by any disability. Moderate fluctuation in the bilirubin level during the course of the disease was common, without any obvious precipitating cause. Bromsulfalein retention was usually marked, even when the patient first sought medical advice.

Studies of Serum Protein. The extreme elevation of serum gamma globulin already noted raised the question of whether the increase represented an abnormal protein with a mobility close to that of normal gamma globulin or an augmentation of normal gamma globulin, perhaps as an intense antibody response to some unrecognized antigen. In an attempt to clarify this point rabbit antisera were prepared against two samples of normal gamma globulin obtained by the Cohn fractionation method as well as gamma globulins obtained from some of the patients. The results suggest that the elevated gamma globulin found in the sera of the patients represented for the most part an elevation of normal gamma globulin.

Analysis of Sternal Marrow. During recent years a considerable amount of clinical and experimental evidence has accumulated suggesting that the development of plasmacytes is associated with production of serum globulins, particularly the gamma globulins.[16–19] In view of these reports a study of the bone marrow was made in nine of the patients. In addition, plasmacyte counts in representative cases were carried out by Dr. R. A. Good. Plasmacytes were quantitated on the basis of counts of 5,000 nucleated marrow cells. These studies revealed neither morphologic nor gross numerical alteration in the plasmacytes or their precursors.

Pathologic Changes in the Liver. The macroscopic findings of the liver at autopsy were somewhat variable but usually a moderately large liver showing a diffuse nodular cirrhosis was found. Considerable variation in the size of the regenerating nodules was noted. In some cases

FIG. 5. Macroscopic appearance of liver (patient C. G.) showing nodular character of the cirrhosis.

scattered nodules had undergone necrosis. The typical finely hobnailed liver was not seen in any of the cases thus far studied. The liver more usually resembled that of so-called classic postnecrotic cirrhosis. (Fig. 5.)

In an earlier paper from this laboratory it was emphasized that patients with liver disease and marked hypergammaglobulinemia may show a large number of plasma cells in the inflammatory exudate of the liver.[1] Nine liver biopsy specimens were available for study from this series. All biopsy specimens were taken at laparotomy and adequate material was available from seven different patients. In five cases the biopsy specimens were obtained during the active phase of the disease at a time when the serum gamma globulin was markedly elevated. Two biopsy specimens were taken in patients who at one time had shown the unusual Cushing-like features but in whom clinical evidence of severe cirrhosis had developed by the time the biopsy specimen was taken. In two patients biopsy specimens were available in both the chronic and the active phase of the disease.

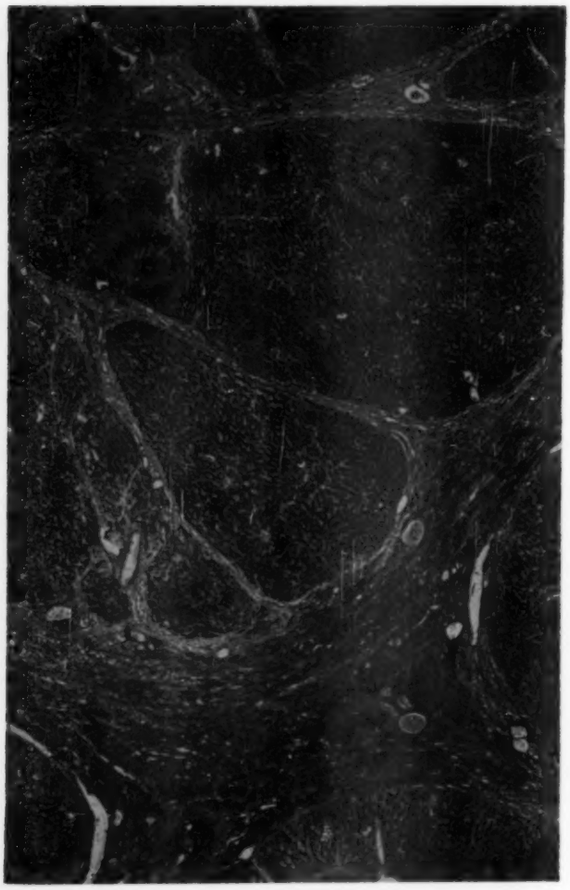

FIG. 6. Photomicrograph of the liver (patient C. G.). Broad bands of fibrous tissue are visible between regenerating nodules. Some distortion of individual lobules is also seen; hematoxylin and eosin, original magnification × 30.

An intensive infiltration of the liver with inflammatory cells was a characteristic finding in patients during the acute stage of the disease when the serum gamma globulin was grossly elevated. Small areas of liver cell necrosis were common. The liver tissue was pervaded by broad strands of fibrous tissue at times isolating areas of normal liver cells. (Fig. 6.)

The cells contributing to the inflammatory exudate in the portal areas were of a variety of types of which the most common were plasmacytes. Fibroblasts, lymphocytes and macrophages were also frequently seen. Figure 7 illustrates the preponderance of mononuclear cells in the exudate. In areas of the liver where the hepatic parenchyma was well preserved, plasmacytes in all stages of development could still be identified within the sinusoids and in the perisinusoidal spaces of Disse.

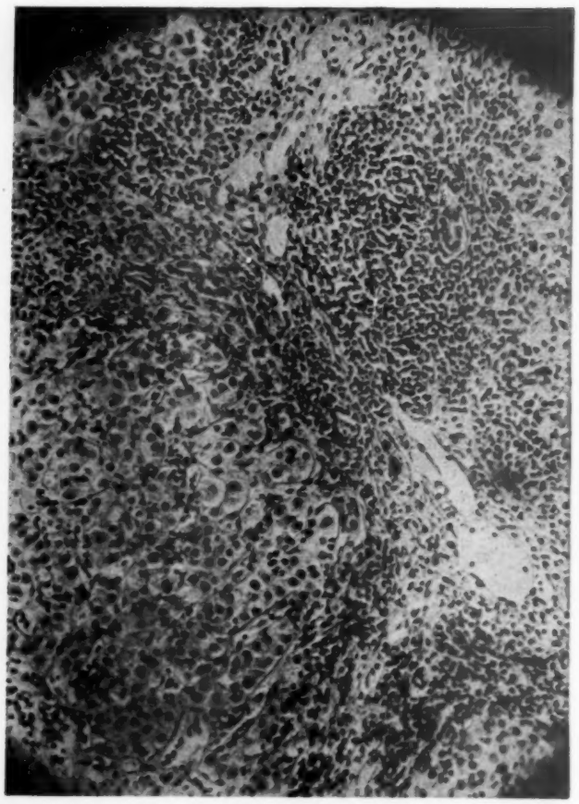

FIG. 7. Photomicrograph of liver (patient M. S., Case 15) showing large number of plasma cells in portal tracts; hematoxylin and eosin, original magnification × 200.

Plasmacyte counts in the liver of several of the patients were carried out. All cells were included in the count with the exception of the hepatic cells and the epithelial cells of the bile ducts. There appeared to be a positive correlation between the markedly elevated gamma globulin in the serum at the time of biopsy and the number of plasmacytes in the liver. In one patient prolonged clinical study and two liver biopsy specimens showed a transition from active disease associated with a high serum gamma globulin and pronounced mononuclear plasma cell infiltration of the liver to progressive cirrhosis with predominantly increased fibrocytic proliferation in the liver.

EFFECT OF ESTROGENS

Four patients gave a history of increased jaundice following administration of estrogen by their attending physician because of delayed menses. In an attempt to investigate the possible hormonal implications of these observations five patients were given a small dose of diethylstilbestrol (1.0 mg./day). In three cases jaundice

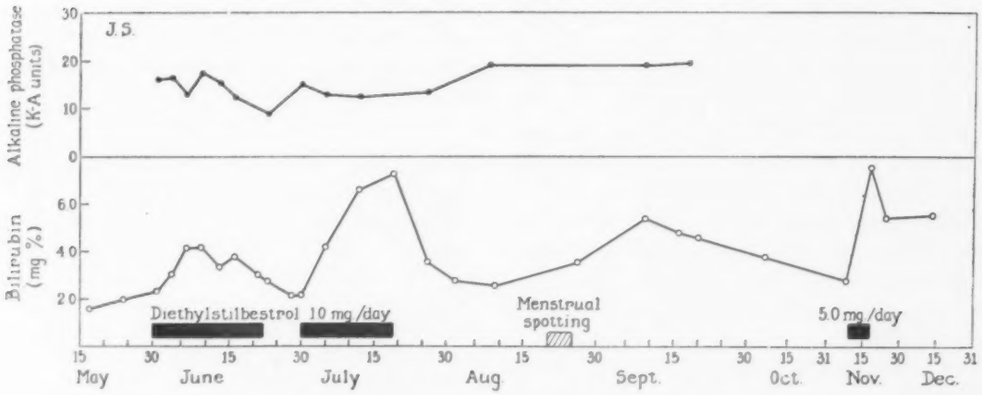

FIG. 8. Effect of diethylstilbestrol on serum bilirubin levels of patient J. S.

increased and in two patients appeared to be greatly intensified. On occasion a rise in the serum bilirubin of some patients occurred at the menstrual period. One patient who, apart from the increased jaundice, showed no untoward effects was given estrogens at timed intervals. On each occasion an increase in the level of serum bilirubin appeared to correlate with administration of the estrogen. (Fig. 8.) No increase in serum bilirubin has been noted in patients with Laennec's cirrhosis after a similar dose of estrogens. However, since an increase in jaundice following administration of estrogens was not invariable, and since the degree of jaundice in these patients is apt to fluctuate, no firm conclusions can yet be drawn. Further work is being undertaken to clarify these preliminary results.

ADRENAL CORTICAL FUNCTION

An evaluation of the adrenal cortical function in some of these patients has already been reported from this laboratory by Bongiovanni and Eisenmenger[2] and will not be described in further detail here. The urinary excretion of reducing corticoids in certain of these patients was distinctly higher than that found in cases of classic Laennec's cirrhosis. Changes in carbohydrate metabolism were also observed.

TREATMENT

The treatment undertaken in this group of patients did not differ significantly from that conventionally advocated in other varieties of chronic liver disease except in the frequent use of cortisone. A nutritious diet insuring an adequate protein intake was combined with salt restriction when indicated. Although avoidance of excessive fatigue was regarded as prudent, strict bedrest was not ordinarily enforced. When first seen many of the patients had been condemned to a regimen of strict bedrest for many months and in consequence were frequently weak, torpid and utterly depressed. In no instance in the present series of cases did a relapse unequivocally follow resumption of graded activity; in fact, the physical and mental improvement of these patients upon resumption of graded activity and return to a gainful occupation was truly remarkable. However, those patients who exhibited periodic febrile episodes were treated with bedrest during the acute episode.

It became apparent during the course of the study that cautious administration of cortisone to patients in the acute stages of the disease was of probable therapeutic value. This was particularly true in those patients in whom generalized manifestations of the disease were present. Following the administration of cortisone the patients frequently felt much improved; the temperature fell to within normal limits and cardiac and respiratory signs diminished. In one patient (H. P.) in whom the electrocardiogram was markedly aberrant administration of cortisone was associated with reversion of the tracing toward normal. The beneficial effects of cortisone in acute exacerbations of the disease encouraged a trial of this medication in those patients in whom periodic acute generalized exacerbations of the disease had occurred in the past. Our limited experience thus far suggests that continued use of small doses of cortisone may be of some value. While on cortisone therapy the patients usually improved symptomatically, the size of the liver and spleen frequently diminished, the serum bilirubin fell

and the serum proteins reverted toward normal. Withdrawal of cortisone from two patients (C. P., H. P.) resulted in prompt clinical and biochemical relapse. In two patients (C. P., H. P.) cortisone has been administered almost uninterruptedly for nearly two years. Although the improvement noted in some of the patients was rather impressive at times there is as yet no conclusive evidence that cortisone modified the disease process or that it will alter the eventual outcome.

CASE REPORTS

CASE 6. Patient C. G. (No. 12454), female, in 1946, at the age of sixteen, noticed gradual onset of migratory muscle pains. These were associated with an increased erythrocyte sedimentation rate. Coincident with the onset of symptoms amenorrhea developed. The following year the patient was given thyroid tablets in an effort to reduce her weight since during the preceding twelve months she had become somewhat obese. At about the same time the development of severe generalized acne was noted, and the patient was observed to be unusually hirsute. Sclerae became yellow, the urine dark and the stools pale. During the next eighteen months the jaundice waxed and waned. Throughout this period the patient felt well, apart from some listlessness. She had no gastrointestinal complaints. Examination in October, 1949, revealed an obese girl with severe generalized acne, jaundice and hirsutism. Several bluish striae were present over the abdomen. The liver and spleen were just palpable. Ascites and edema were absent. Laboratory examination revealed a total serum protein between 7.0 and 8.1 gm. per cent and a serum albumin between 2.7 and 3.2 gm. per cent. The results of the zinc turbidity test remained fairly constant between 40 and 42 units. The serum bilirubin fell somewhat during her hospital stay but rose sharply on administration of estrogens (diethylstilbestrol 1.0 mg. daily). (Fig. 8.) In May, 1950, ascites and ankle edema developed. Although the peripheral edema responded to salt restriction, the ascites persisted and the patient's course was progressively downhill. In November, 1950, the first esophageal hemorrhage occurred. This was controlled by esophageal tamponade and replacement transfusions. The patient continued to deteriorate, however, lapsed into a pre-comatose state and finally died in coma following peritoneal infection and a further esophageal hemorrhage.

At autopsy the liver weighed 1,300 gm. and showed gross irregular nodularity. The nodules were separated by broad strands of grayish connective tissue. (Fig. 6.) Large numbers of proliferating plasma cells were seen in the portal tracts and to a lesser extent throughout the liver cells. Many small areas of fresh liver cell necrosis were seen. The bile canaliculi showed moderate proliferation. The spleen weighed 925 gm. There was an increase in stem and plasma cells in the intersinusoidal spaces. No "onion-skin" lesions were seen. The lymph nodes also showed definite proliferation of stem and plasma cells.

CASE 10. L. B. (No. 12243), female, at the age of thirty-two, was noted to have jaundice in February, 1943, approximately three months after the development of erythema multiforme and of painful swelling of joints, particularly of the ankles. Fever which coincided with the onset of the joint pains rose as high as 103°F. during April, 1943. The serum total protein was elevated to 10.2 gm. per cent. The arthritis and liver disease progressively became worse, the patient continued to have jaundice throughout 1944. There were two further episodes of erythema multiforme. Histopathologic examination of one of the skin lesions and a muscle biopsy specimen showed no evidence of periarteritis nodosa. In January, 1945, edema and moderate ascites developed and the patient was admitted to the Rockefeller Hospital for the first time. Physical examination showed a well nourished woman with swelling and tenderness of the left knee, both ankles and the right wrist. The liver was enlarged six fingerbreadths below the costal margin and was firm. The spleen was enlarged four fingerbreadths below the left costal margin. There were no spider angiomas. Laboratory tests revealed a serum total protein of 8.9 gm. per cent and globulin of 5.6 gm. per cent. The electrophoretic pattern revealed a gamma globulin of 5.0 gm. per cent. The serum bilirubin was 1.8 mg. per cent. At laparotomy, a biopsy specimen of the liver showed nodular cirrhosis with considerable invasion of the liver by mononuclear cells, particularly plasma cells.

The patient's hospital course was characterized by daily episodes of fever reaching 103°F., and marked swelling and tenderness of the joints. Because of the further development of ascites, concentrated human serum albumin was given. Considerable general improvement occurred, and the ascites gradually disappeared. The febrile episodes subsided in 1946 but the joints showed chronic arthritic changes which interfered with walking. (Fig. 2.)

During 1948 and 1949 the serum albumin level remained low despite albumin therapy and ascites proved somewhat difficult to control. In February, 1949, a second laparotomy was carried out and a biopsy specimen removed. At this stage the serum gamma globulin concentration had fallen to approximately 3.5 gm. per cent. The liver now showed more advanced cirrhosis and the cellular infiltration previously seen had decreased considerably. Administration of ACTH, 100 mg. per day for six days, produced relief from the arthritis, a rise in the serum albumin and a fall in serum gamma globulin. These effects persisted for three weeks after therapy was stopped; thereafter the patient reverted to her pretreatment condition. In December, 1950, she received

a course of cortisone for the severe joint pains. During this treatment she had slight hematemesis. She responded initially to conservative therapy and replacement transfusions but following further hematemesis lapsed into hepatic coma and died.

CASE 24. H. P. (No. 12167), female, at the age of nineteen and during the winters of 1945 and 1946 had frequent upper respiratory tract infections associated with fever and diffuse arthralgias of the knees, ankles and wrists. In February, 1946, the insidious onset of symptomless jaundice associated with intermittent fever was noted. In May, 1946, the liver was enlarged six fingerbreadths and the spleen was just palpable. Arthralgia persisted and several rheumatic nodules developed. Biochemical examination revealed a serum total protein of 11.0 gm. per cent, albumin 2.5 gm. per cent, globulin 8.5 gm. per cent. At laparotomy a biopsy specimen revealed cirrhosis of the liver and the spleen was noted to be enlarged. Apart from occasional episodes of severe spontaneous bleeding from the gums, the patient remained fairly well. In November, 1950, large esophageal varices were noted. Four months later severe esophageal hemorrhage occurred. Subsequently a portacaval shunt was successfully performed.

Throughout 1950 and 1951, the patient experienced acute episodes of fever, precordial pain and shortness of breath. Clinical examination revealed a gallop rhythm, a pericardial rub, cardiac enlargement and small bilateral pleural effusions. These symptoms, however, subsided over a period of one to two weeks. Another episode occurred in March, 1952. Numerous blood cultures proved sterile. Salicylates and antibiotics had no effect on either the fever or the symptomatology. On two occasions, however, L.E. cells were found in the blood. In April, 1952, there was a marked exacerbation of all previous symptoms, accompanied with a flare-up of arthritis and general deterioration in her status. She was given a trial of ACTH with immediate improvement. The fever defervesced, the arthralgia disappeared and the cardiac size diminished. Laboratory investigation revealed that the serum bilirubin had fallen from approximately 10.0 mg. per cent to about 4.0 mg. per cent, the serum albumin showed some slight increase accompanied with a slight fall in the serum globulin. The patient was finally stabilized on a regimen of 50 mg. cortisone daily. In 1954 she was married and in 1955 was successfully delivered of a normal infant. There has been little change in her clinical or biochemical condition during the past two years, and she has continued to lead a useful life. Her daily dose of cortisone varies between 25 and 50 mg. daily.

DISCUSSION

Sporadic reports of patients with a clinical syndrome similar to that of the present series have appeared in the literature.[20–23] In most of the reported cases the etiology was unknown. In others a history of acute infectious hepatitis was obtained and the virus of infectious hepatitis was held responsible for the development of hepatic cirrhosis. In patients in whom no history of hepatitis was obtained it has often been assumed that these patients suffered from a cryptic form of acute hepatitis which gave rise to chronic liver disease. Although this assumption can be supported by many reports in the literature of isolated cases of infectious hepatitis with subsequent development of hepatic cirrhosis,[24,25] it should be pointed out that such an explanation has not always been regarded as entirely satisfactory.[22] Moreover, recent studies by Zieve and coworkers[26] suggest that the true incidence of hepatic cirrhosis following acute infectious hepatitis may be considerably less than considered heretofore. In the present survey patients with severe cirrhosis after classic infectious hepatitis were not included. Six such patients were observed during the period encompassed by this study. Of the main group of twenty-six patients, seven gave a history possibly compatible with acute hepatitis; of these six were women. In the remaining nineteen cases (73 per cent) no specific etiologic agent could be implicated. None of the patients in whom a negative history for hepatitis was obtained had had any febrile illness associated with minor gastrointestinal complaints which could be interpreted as possible hepatitis in the past. Several of these patients were skin-tested for possible evidence of previous hepatitis; none was found.[27]

Sex incidence of post-hepatitis cirrhosis in young adults has received relatively little notice in the past. It was to be anticipated that during and immediately after the last war most cases of posthepatic cirrhosis would occur in men.[24,25,28] However, this apparent predominance in men may not exist under peace time conditions. Sex incidence of post-hepatitis cirrhosis of the liver is still a controversial subject and is confused further by the frequent use of the term post-necrotic cirrhosis synonymously with post-hepatitis cirrhosis. In 1947 Witts and coworkers[7] pointed out that of their patients with post-necrotic cirrhosis who gave no history of acute infectious hepatitis and in whom the onset of the disease was insidious, three times as many women as men were affected. Baggenstoss and Stauffer[29] in this country also reported a predominance of

women in cases of post-hepatitis cirrhosis, as has Watson[5] also. However, there is no complete unanimity of opinion on this point and Ratnoff and Patek[30] in a recent review of cases of post-necrotic cirrhosis state that "there is no clearcut evidence that post necrotic cirrhosis in man is more frequent in one sex than the other."

The incidence of arthralgia in post-hepatitis cirrhosis is uncertain. Watson[5] suggests that arthralgia may occur with some frequency in chronic hepatitis. This has not been particularly noted by other investigators. No history of hepatitis was obtained in eight of eleven of our cases in whom symptoms developed relating to the joints. In one detailed case reported in the literature, in which many of the symptoms common to this syndrome including arthralgia were present, no history of viral hepatitis could be elicited.[22]

Selection of cases might be held responsible for the high proportion of women in the cases of cirrhosis of obscure etiology observed at this clinic. Certainly a few young women were referred because of our known interest in this variety of liver disease. However, special efforts were made during this period to obtain patients with post-hepatitis cirrhosis from Veterans Hospitals and these men in fact accounted for some of the cases in the present series. The true sex incidence of this disorder must await further experience based upon extended studies from general hospitals in different geographic areas.

Extreme hypergammaglobulinemia is an uncommon though well recognized feature of some cases of cirrhosis unquestionably due to acute infectious hepatitis.[25,28,31] Although this occurs in both sexes, it is noteworthy that many of the reported cases have been in young women. Baggenstoss and Stauffer[29] reported that of fourteen patients with post-hepatitis cirrhosis of the liver and increased values for serum globulin, eleven were women. However, the two patients with the highest values for serum globulin also were women. These results suggest that if one of the etiologic agents responsible for this condition is the virus of infectious hepatitis, specific endocrine influence present in young women modify its morbid effects to such an extent that an unusual form of the disease may become manifest.

The sex incidence, the generalized nature of the disease in certain persons, the involvement of joints, pericardium and lungs as well as liver, raises the possibility that some other disorder, possibly related to the collagen diseases, may play an important part in the disease process in some instances. The finding of typical L.E. cells in the blood of one patient and the prompt alleviation of many of the signs and symptoms of the acute generalized episodes by the administration of cortisone may give some support to this concept. Joske et al.[32] have recently reported the apparent presence of L.E. cells in the blood of two patients suffering from "active chronic viral hepatitis." Further studies of the L.E. phenomenon in the acute febrile stages of the disease are clearly indicated. Many of the signs and symptoms of classic lupus erythematosus are lacking in these patients, and cirrhosis, although occasionally seen in disseminated lupus,[33] is a rare finding.

Despite the heterogeneous nature of the disease process in the group of patients studied, there appear to be sufficient similarities within the group to warrant their consideration together. To be sure, similar manifestations occasionally follow acute infectious hepatitis but more commonly the etiology appears less certain and multiple unrecognized etiologic factors may initiate the disease process.

SUMMARY

1. Attention has been drawn to a group of patients suffering from a severe form of hepatic cirrhosis, the majority of whom were young women. Certain features not usually observed in patients with Laennec's cirrhosis were commonly seen. These features included arthritis, obscure febrile episodes and, occasionally, hormonal disturbances. Striking improvement followed the use of cortisone in some cases.

2. Laboratory investigations in the acute stages of the disease usually revealed an extremely high serum gamma globulin and an increase in the plasma cells of the liver.

3. The possibility that specific endocrine influences, present in young women, modify the usual course of infectious hepatitis is discussed. In most of the patients the etiology of the disease process was uncertain.

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REFERENCES

1. Kunkel, H. G., Ahrens, E. H., Jr., Eisenmenger, W. J., Bongiovanni, A. M. and Slater, R. J. Extreme hypergammaglobulinemia in young women with liver disease. *J. Clin. Investigation*, 30: 654, 1951.
2. Bongiovanni, A. M. and Eisenmenger, W. J. Adrenal cortical metabolism in chronic liver disease. *J. Clin. Endocrinol.*, 11: 152, 1951.
3. Himsworth, H. P. Lectures on the Liver and its Diseases, 2nd ed. Cambridge, 1950. Harvard University Press.
4. Good, R. A. Personal communication.
5. Watson, C. J. Some observations on the recognition and treatment of the common forms of hepatic cirrhosis. *Minnesota Med.*, 35: 125, 1952.
6. Sherlock, S. Diseases of the Liver and Biliary System. Springfield, Illinois, 1955. Charles C Thomas.
7. Kelsall, A. R., Stewart, A. and Witts, L. J. Subacute and chronic hepatitis. *Lancet*, 2: 195, 1947.
8. Eder, H. A., Russ, E. M., Pritchett, R. A. R., Wilber, M. M. and Barr, D. P. Protein-lipid relationships in human plasma: in biliary cirrhosis, obstructive jaundice and acute hepatitis. *J. Clin. Investigation*, 24: 1147, 1955.
9. Waldenström, J. Personal communication.
10. Capps, R. B., Bennett, A. M. and Stokes, J., Jr. Endemic infectious hepatitis in an infant's orphanage. I. Epidemiologic studies in student nurses. *Arch. Int. Med.*, 89: 6, 1952.
11. Neefe, J. R. Viral hepatitis. Problems and progress to 1954. *Am. J. Med.*, 16: 710, 1954.
12. Slater, R. J. Investigation of an infant born of a mother suffering from cirrhosis of the liver. *Pediatrics*, 13: 308, 1954.
13. Ahrens, E. H., Jr., Payne, M. A., Kunkel, H. G., Eisenmenger, W. J. and Blondheim, S. H. Primary biliary cirrhosis. *Medicine*, 29: 299, 1950.
14. Kunkel, H. G. Estimation of alterations of serum gamma globulin by a turbidimetric technique. *Proc. Soc. Exper. Biol. & Med.*, 66: 217, 1947.
15. Hanger, F. M. The meaning of liver function tests. *Am. J. Med.*, 16: 565, 1954.
16. Bing, J. and Plum, P. Serum proteins in leucopenia. *Acta med. Scandinav.*, 92: 415, 1937.
17. Jarrold, R. and Vilter, R. W. Hematologic observations in patients with chronic hepatic insufficiency. *J. Clin. Investigation*, 25: 286, 1949.
18. Good, R. A. and Campbell, B. The relationship of the numbers of bone marrow, plasma and cells to the concentration of gamma globulin in rheumatic fever. *Am. J. Med.*, 9: 330, 1950.
19. Good, R. A. Studies on agammaglobulinemia. II. Failure of plasma cell formation in the bone marrow and lymph nodes of patients with agammaglobulinemia. *J. Lab. Clin. Med.*, 46: 167, 1955.
20. Amberg, S. Hyperproteinemia associated with severe liver damage. *Proc. Staff Meet., Mayo Clin.*, 17: 360, 1942.
21. Cullinan, E. R. Idiopathic jaundice (often recurrent) associated with subacute necrosis of the liver. *St. Barth. Hosp. J.*, 69: 55, 1936.
22. Case records of the Massachusetts General Hospital, No. 34402. *New England J. Med.*, 239: 519, 1948.
23. Clinico-pathological Conference. *Am. J. Med.*, 7: 114, 1949.
24. Sherlock, S. Post hepatitis cirrhosis. *Lancet*, 1: 817, 1948.
25. Kunkel, H. G. and Labby, D. H. Chronic liver disease following infectious hepatitis in cirrhosis of the liver. *Ann. Int. Med.*, 32: 433, 1950.
26. Zieve, L., Hill, E., Nesbitt, S. and Zieve, B. The incidence of residuals of virus hepatitis. *Gastroenterology*, 25: 495, 1953.
27. Henle, G., Drake, M., Henle, W. and Stokes, J., Jr. A skin test for infectious hepatitis. *Proc. Soc. Exper. Biol. & Med.*, 73: 603, 1950.
28. Volwiler, W. and Elliott, J. A., Jr. Late manifestations of epidemic infectious hepatitis. *Gastroenterology*, 10: 349, 1948.
29. Baggenstoss, A. H. and Stauffer, M. H. Post hepatitis and alcoholic cirrhosis. *Gastroenterology*, 22: 157, 1952.
30. Ratnoff, O. D. and Patek, A. J. Post necrotic cirrhosis of the liver. *J. Chronic Dis.*, 1: 266, 1955.
31. Zimmerman, H. J., Heller, P. and Hill, R. P. Extreme hyperglobulinemia in subacute hepatic necrosis. *New England J. Med.*, 244: 245, 1948.
32. Joske, R. A. and King, W. E. The LE-cell phenomenon in active chronic viral hepatitis. *Lancet*, 11: 477, 1955.
33. Harvey, A. M., Shulman, L. E., Tumulty, P. A., Conley, C. L. and Schoenrich, E. H. Systemic lupus erythematosus: review of the literature and clinical analysis of 138 cases. *Medicine*, 33: 4, 1954.

Portal Hypertension Due to Chronic Occlusion of the Extrahepatic Portion of the Portal Vein: Its Relation to Ascites*

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THE mechanism of formation of ascites has intrigued investigators for a long time. In a recent review of the subject Hyatt and Smith[1] gave an excellent account of both the clinical and experimental conditions under which ascites occurs, together with a physiologic appraisal of the factors involved. Concerning portal obstruction they stated: "Since liver disease with ascites is attended by portal congestion, it might be expected that isolated portal obstruction could likewise provoke ascites. Indeed, clinical observation has frequently indicated that variable degrees of ascites may result from portal occlusion due to endophlebitis (thrombosis) or external compression. However, systematic studies of the ascites arising from portal vein occlusion are notably few." Our investigation was carried out in an effort to supply such a systematic study at necropsy.

MATERIAL AND METHODS

All cases studied at necropsy in which the anatomic diagnosis was occlusion of the portal vein were reviewed. Two hundred fifteen cases were found. All cases of recent thrombosis or of thrombosis involving only isolated intrahepatic branches of the portal vein were discarded. All cases of portal thrombosis with ascites were excluded if concomitant cirrhosis of the liver, peritoneal carcinomatosis, chronic peritonitis, renal disease, congestive heart failure, obstruction of hepatic veins, Meigs' syndrome, myxedema or obstruction of the inferior vena cava above the liver was present. In other words, if any condition or lesion other than occlusion of the portal vein which in itself might account for the ascites was present, that case was excluded. This method of selection uncovered fifteen cases of ancient thrombosis of the portal vein uncomplicated by any other condition that might cause ascites. In five of these cases long-standing ascites was present and in ten no ascites was present. The pathologic findings of these two groups were studied and compared to determine if possible the factors responsible for the presence or absence of ascites. In order to indicate the clinical findings and course, brief summaries are included of one representative case in which there was no ascites and of all five cases in which ascites developed.

PORTAL OBSTRUCTION WITHOUT ASCITES (TEN CASES)

In this group there were five men and five women. Their ages ranged from ten to forty-three years, with a mean age of thirty years.

CASE 1. The patient, a 30 year old bookkeeper, was first admitted to the Clinic in February, 1940, because of recurring episodes of hematemesis and melena since 1928. Splenectomy had been carried out elsewhere in 1929 and the spleen was said to have been nine times the normal size. The patient had experienced further episodes of gastrointestinal bleeding in 1937, 1938 and 1939.

Examination at the Clinic gave essentially normal results except for pallor of the skin. The urine was normal. The concentration of hemoglobin was 9.6 gm. per 100 cc. of blood. Erythrocytes numbered 4,160,000 and leukocytes 5,700 per cubic millimeter. A stained film of the blood revealed a macrocytic hypochromic type anemia. A sulfobromophthalein test of liver function revealed no retention of dye. The serum bilirubin was 0.8 mg. per 100 cc. and gave an indirect reaction to the van den Bergh test. Varices were demonstrated in the lower part of the esophagus both roentgenologically and on esophagoscopic examination. Four injection treatments to occlude these veins were carried out through the esophagoscope in February, 1940, and again in December, 1940. However, bleed-

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FIG. 1. (*a*) Old canalized thrombus of portal vein with numerous accessory portal veins in the hepatoduodenal ligament; no ascites. (*b*) Hematoxylin and eosin, × 6.5.

ing recurred within a few months following both series of injections.

The patient returned to the Clinic in January, 1946, when he was thirty-six years old. Examination and the results of laboratory studies were essentially the same as before. The value for total serum proteins was 5.6 gm. with 3.6 gm. of albumin and 2.0 gm. of globulin per 100 cc. In spite of five more injection treatments to occlude the dilated esophageal veins the patient soon died of massive hemorrhage of the upper gastrointestinal tract.

At necropsy an old organized, calcified and canalized thrombus of the portal vein was found. There were numerous large accessory portal (hepatopetal) veins in the hepatoduodenal ligament. The liver weighed 1,777 gm. Esophageal and gastric varices were large and numerous. One of the gastric varices had ruptured, and there was 3,500 cc. of blood in the stomach and small intestine. Death was attributed to the hemorrhage from the ruptured gastric varix.

Cause of Death. The principal or underlying cause of death was considered to be old thrombosis of the portal vein in all ten cases. The immediate causes of death were esophageal varices with rupture and hemorrhage in five cases and gangrene of the jejunum, necrosis of the liver, postoperative intraperitoneal hemorrhage, empyema and pulmonary embolism in one case each.

Pathologic Findings. The spleen was enlarged in all ten cases but varied in weight from 500 to 1,510 gm., with a mean weight of 829 gm. for the six cases in which the weight was recorded. The liver was usually smaller than normal. Excluding the single case of extensive infarction of the liver, the mean weight was 1,587 gm. for the eight cases in which the weights were obtained. At necropsy evidence of extrahepatic (hepatofugal) collateral circulation was obtained in most cases, and in nine cases gastric or esophageal varices were observed.

Hepatopetal or accessory portal veins which shunted blood around the portal obstruction to enter the liver were prominent in nine of the ten cases. These veins were numerous in the hepatoduodenal ligament and are included in the so-called accessory portal veins of Sappey. Occasionally they were so numerous that they resembled hemangioma of the lesser omentum. (Fig. 1.) Pick[2] in his report interpreted these as being hemangiomas. The deep cystic veins, epiploic veins and veins of the hilus of the liver, including the vasa vasorum of the portal vein and hepatic artery, and the veins in the wall of the common bile duct are included among these accessory portal veins. (Fig. 2.) Less frequently noted as increased in number and size were the diaphragmatic veins, the veins in the suspensory ligament of the liver and the paraumbilical veins.

Histologic examination of the portal vein revealed obliteration of the lumen by fibrous connective tissue which was traversed by numerous new venous channels. Collections of lymphocytes, phagocytes containing yellow pigment and lipophages, and deposits of calcium were occasionally observed in the fibrotic mass and in the

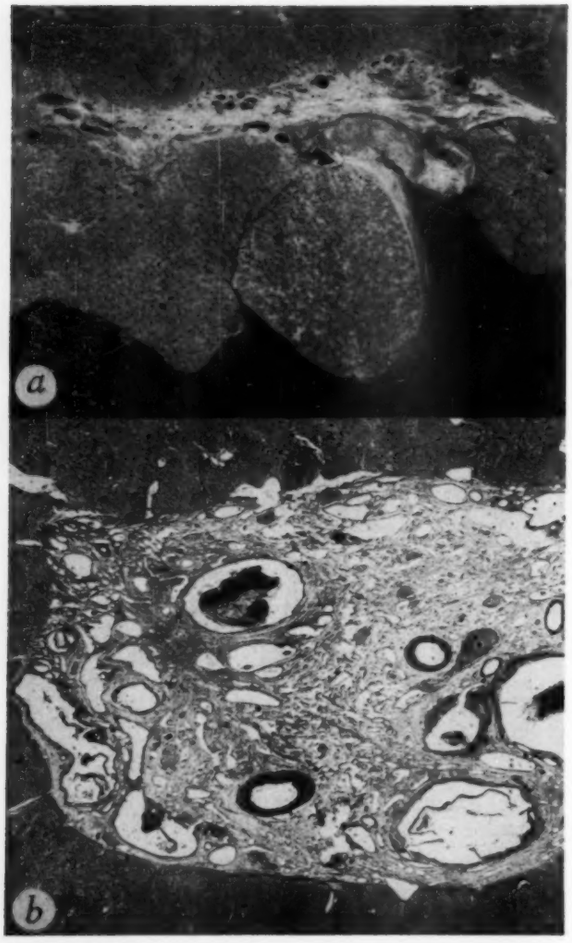

FIG. 2. (*a*) Accessory portal veins within the liver above the organized thrombus; no ascites. (*b*) Hematoxylin and eosin, original magnification × 6.

wall of the vein. A ten year old girl had congenital hypoplasia of the portal vein. Occasionally, recent thrombi in various stages of organization were found in the new venous channels. The wall of the portal vein usually revealed fibrosis of all layers and the muscular fibers were generally atrophied. This has been called phlebosclerosis by some authors but we interpreted this appearance as a reaction to the organizing thrombus.[3] Large venous channels were numerous in the wall of the portal vein and in the surrounding connective tissue of the hepatoduodenal ligament. These were interpreted as collateral pathways for portal blood which undoubtedly developed or enlarged after the original occlusion. The same fibrous type of occlusion occasionally involved the splenic and mesenteric veins but more frequently these vessels were the site of recent thrombi.

Histologic examination of the liver revealed evidence of mild chronic passive congestion with pigmentation and atrophy of hepatic cells in the neighborhood of the central vein in eight cases. Mild infiltration with fat occurred in four cases, and central necrosis and increased numbers of lymphocytes in the periportal spaces in two cases each. An infarct of the liver and atrophy of the left lobe of the liver were each observed once.

Sections of the spleen were available in six cases. These sections revealed severe fibrosis of the pulp with dilated sinuses like those in the Banti type splenomegaly. Siderofibrotic nodules were observed in two cases.

Review of the histologic sections of the kidneys in these cases yielded no examples of glomerulonephritis. Mild to moderate proliferation of the endothelial cells of the glomerular capillaries was noted in two cases but these changes were not considered severe enough for a diagnosis of glomerulonephritis. Acute tubular damage with varying stages of degeneration and necrosis of tubular epithelium and interstitial edema were observed in the case of the patient who died in shock. So-called metastatic calcification was found in six of the ten cases; the significance of this finding is unknown.

Histologic examination of the adrenal glands revealed narrow cortices, indicating atrophy of the cortical cells, in five cases. The atrophy of the cells generally appeared most pronounced in the zona fasciculata. Necrosis of the cortical cells and focal disorganization of the zona fasciculata occurred in one case each.

PORTAL OBSTRUCTION WITH ASCITES (FIVE CASES)

In this group there were two men and three women. Their ages ranged from twenty-five to sixty-two years, with a mean age of forty-five years. In all five cases ascites had been present for six to twenty-four months before death.

CASE II. The patient, a twenty-five year old farmer, was admitted to the Clinic in September, 1918, because of swelling of the abdomen which had been present since the age of two years when enlargement of the spleen had been discovered. The abdominal swelling had become more noticeable during the three years prior to admission. Hematemesis had occurred twice, three months and six weeks before admission. On the more recent occasion the patient had vomited two quarts of blood. In the preceding six months he had been weak, had lost thirty pounds and had undergone abdominal paracentesis eight times with removal of large amounts of fluid each time. Two and one-half

months before admission swelling of the legs developed which subsided in a few weeks. No history of jaundice was obtained.

Examination revealed great enlargement of the spleen; the abdomen was much distended with fluid. There was no peripheral edema. Urinalysis revealed no abnormalities. The concentration of hemoglobin in the blood was 24 per cent (Dare); erythrocytes numbered 2,420,000 and leukocytes 1,600 per cubic millimeter.

A diagnosis of Banti's syndrome was made. Following blood transfusion, splenectomy was carried out at which time the abdomen contained 10 L. of fluid. The spleen was much enlarged and weighed 2,005 gm. The patient died sixteen days after operation.

At necropsy an old organized and canalized thrombus occluded the main trunk of the portal vein. There were only a few small accessory portal veins (hepatopetal collateral veins) in the hepatoduodenal ligament. Recent thrombi were present in the splenic and mesenteric veins. Edema and gangrene of many loops of the small intestine were noted. The abdomen contained approximately 10 L. of ascitic fluid. The immediate cause of death was considered to be recent thrombosis of the superior mesenteric vein with gangrene of the small intestine.

CASE III. The patient, a forty-eight year old housewife, was admitted to the Clinic in January, 1938, because of enlargement of the spleen which had been discovered five years previously. For six months before admission she had noticed slight loss of energy, slight discomfort across the upper part of the abdomen and some increase in the size of the abdomen.

A greatly enlarged spleen, extending down to the crest of the ilium on the left side was palpated. The liver was not palpable. The abdominal distention was thought to be due to ascites. No edema of the ankles was noted. Urinalysis gave negative results. The value for hemoglobin was 13.1 gm. per 100 cc. of blood; erythrocytes numbered 4,850,000 and leukocytes 4,900 per cubic millimeter. The sulfobromophthalein test of liver function revealed retention of dye, grade 1 (between 6 and 12 per cent) at the end of one hour. The value for serum bilirubin was 1.8 mg. and the van den Bergh reaction was indirect. Roentgenographic examination of the esophagus did not reveal varices.

A clinical diagnosis of Banti's syndrome was made. At the time of splenectomy and omentopexy a moderate degree of ascites was found. The spleen was greatly enlarged, weighing 2,270 gm. An incidental finding at the operation was a leiomyoma of the stomach, 15 by 20 cm. in diameter, which was removed. Massive ascites developed during the postoperative period and was evacuated by means of paracentesis. The patient died on the nineteenth postoperative day.

Necropsy disclosed an old organized and canalized thrombus of the portal and splenic veins. (Fig. 3.)

FIG. 3. Case III. Old thrombosis of portal vein at hilus of liver. Note small size and paucity of accessory portal veins; ascites present.

Recent thrombi were observed in the splenic, gastric and inferior mesenteric veins also. The accessory portal veins in the hepatoduodenal ligament were numerous and dilated. There was thrombosis of the left subclavian and axillary veins with pulmonary emboli. Atrophy of the liver was noted, the liver weighing only 1,382 gm. There were varices in the submucosa of the stomach and 1,500 cc. of ascitic fluid. Death was attributed to generalized thrombosis of the veins and pulmonary embolism.

CASE IV. The patient, a thirty-six year old housewife, was admitted to the Clinic in December, 1916, because of weakness and swelling of the abdomen of about six months' duration. Ten years previously she had had an attack of acute upper abdominal pain associated with fever. Three years prior to admission she had had an episode of left epigastric pain associated with vomiting which lasted one day but she had never had jaundice. For seven years she had had intermittent episodes of diarrhea lasting as long as one month with as many as two to four stools per day. She had never noticed bloody or tarry stools. During the past six months the size of her abdomen had increased so much that she was unable to fit into her clothes. Medical examination, one month prior to admission at the Clinic, dislcosed an enlarged spleen and ascites. One gallon of fluid was removed by paracentesis, but the fluid reaccumulated rapidly.

Examination revealed that the abdomen was distented with fluid and the spleen extended almost to the brim of the pelvis on the left side. There was no peripheral edema. Urinalysis was normal. The value for hemoglobin was 70 per cent; erythrocytes numbered 4,000,000 and leukocytes 8,800 per cubic millimeter of blood. At the time of operation, the excised spleen weighed 1,480 gm. and several gallons of

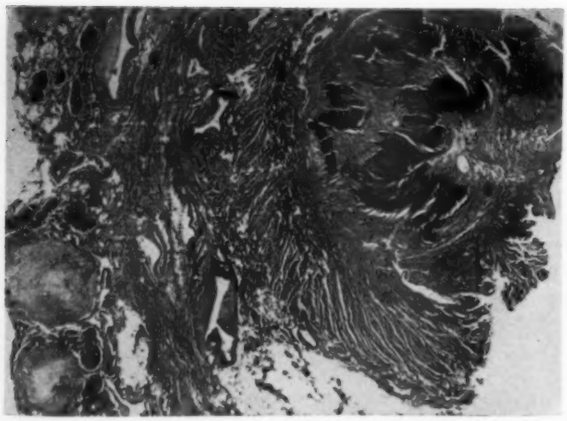

FIG. 4. Case IV. Old organized and calcified thrombus of portal vein; ascites present. Note moderate number of accessory portal veins and lack of canalization; hematoxylin and eosin, original magnification × 12.

ascitic fluid were removed. The patient died seven days later.

At necropsy, marked intimal thickening and fibrosis of the portal vein were found and the lumen of the portal vein was occluded by an organized and calcified thrombus with little evidence of canalization. (Fig. 4.) There were a moderate number of hepatopetal (accessory portal) veins in the wall of the vein and the surrounding connective tissue. The peritoneal cavity contained several liters of turbid, blood-tinged fluid, and the loops of small intestine beneath the incision were covered by fibrinous exudate. The stomach, small intestine and colon were all severely distended with gas. Death was attributed to localized peritonitis and ileus.

CASE V. The patient, a sixty-two year old farmer, was admitted to the Clinic in May, 1919. He had had two episodes of gastrointestinal bleeding, one two years previously and the other nine months previously. The first episode of bleeding was characterized by hematemesis. In the second episode melena occurred for three weeks and was associated with abdominal ascites for which abdominal paracentesis was required. During the nine months prior to admission abdominal paracentesis had been carried out five times.

Examination disclosed evidence of anemia, considerable enlargement of the spleen and ascitic fluid in the abdomen. There was no peripheral edema. Urinalysis revealed no significant abnormalities. The value for hemoglobin was 31 per cent. Erythrocytes numbered 2,160,000 and the leukocytes 2,000 per cubic millimeter of blood.

After several blood transfusions the patient underwent splenectomy. The spleen, which was considerably enlarged, weighed 820 gm. The abdomen contained a large quantity of fluid. The patient died one day after operation.

At necropsy there was a marked fibrous thickening of the walls of the portal, superior mesenteric and splenic veins at their junction. The lumen of the portal vein at this point was only 5 mm. in diameter. The lesion was interpreted as an old organized thrombus. No accessory portal veins were described but a large collateral vein was observed extending from a plexus of dilated veins in the splenic fossa to the left spermatic vein. The liver was estimated as two-thirds its normal size. The peritoneal cavity contained more than 2 L. of blood but the source of the hemorrhage could not be found. Death was attributed to postoperative hemorrhage.

CASE VI. The patient, a housewife aged forty-seven years, was first admitted to the Clinic in September, 1929, because of recurrent swelling of the face for one year and goiter.

Examination revealed a swollen face and a thyroid symmetrically enlarged to a moderate degree. The pulse rate was 110 beats per minute. Examination of the abdomen and pelvis revealed a left ovarian cyst about the size of an orange. Moderate edema of the ankles was present. The urine was normal. The value for hemoglobin was 13.5 gm. per 100 cc. Erythrocytes numbered 4,190,000 and leukocytes 12,600 per cubic millimeter of blood. The basal metabolic rate was +15 per cent. A clinical diagnosis of exophthalmic goiter was made; subtotal thyroidectomy was carried out. Microscopic examination of the removed tissue revealed cystic degenerative colloid and fetal adenomas in a colloid thyroid. One month after thyroidectomy left oophorectomy was performed with the removal of a multilocular ovarian cyst measuring 14 by 8 by 7 cm. and containing a hemorrhagic fibrous hyaline cystic degenerating colloid and fetal thyroid adenoma. This tumor of the ovary was considered to be a teratoma and weighed 210 gm. At the time of the operation the abdomen was found to contain several quarts of milky ascitic fluid but further abdominal exploration revealed no abnormalities.

Following this operation convalescence was satisfactory except for continued ascites. When the patient returned to the Clinic in October, 1931, at the age of forty-nine years, she stated that abdominal paracentesis with the removal of as much as 12 L. of fluid at a time had been required on an average of every two to three weeks during the two years since oophorectomy. The fluid was clear or slightly cloudy. Examination at this time revealed marked ascites but no abdominal organs or masses were felt. There was no edema of the legs. Several urinalyses showed a moderate degree of albuminuria and a considerable number of erythrocytes in the urinary sediment. Examination of the blood revealed 12.3 gm. of hemoglobin per 100 cc. and 14,000 leukocytes per cubic millimeter. A sulfobromophthalein test of liver function revealed no retention of dye. The value for serum bilirubin was 1.1 mg. per 100 cc. and the van den Bergh reaction

was indirect. The values for total serum protein were 6.6 gm. per 100 cc. on one occasion and 6.2 gm. with 3.4 gm. of serum albumin and 2.8 gm. of serum globulin on another. The basal metabolic rate was −4 per cent. Roentgenograms of the thorax revealed no abnormalities.

An exploratory operation was performed in October, 1931, at which time a large amount of clear, slightly orange-colored fluid was evacuated from the abdominal cavity. Exploration of the entire abdomen and pelvis revealed no abnormalities and no cause for the ascites. Approximately two months following this procedure the patient experienced sudden severe abdominal pain, went into shock and died within forty-eight hours.

At necropsy a well organized and fibrotic thrombus with little canalization was found in the portal vein. (Fig. 5.) Only a few small accessory portal (hepatopetal) veins were observed in the hepatoduodenal ligament. There was a recent thrombus in the superior mesenteric vein with acute infarction of the jejunum. Esophageal varices were prominent and the liver was small, weighing 1,560 gm. The spleen appeared to be the site of chronic infarction and weighed only 35 gm. The abdomen contained about 10 L. of ascitic fluid. Death was attributed to recent thrombosis of the superior mesenteric vein with infarction of the jejunum.

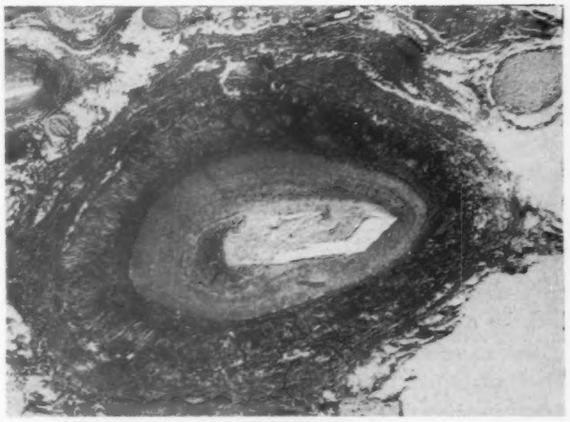

FIG. 5. Case VI. Old organized thrombus of portal vein; ascites present. Note lack of canalization of thrombus and paucity of accessory portal veins; elastic van Gieson stain, original magnification × 12.

Edema, Ascites and Causes of Death. On clinical examination during their terminal illness none of the patients had edema of the lower extremities; however one patient (Case II) had had transient edema of the legs several weeks previously and another patient (Case VI) had had edema of the legs two years previously but this had subsided after removal of the ovarian tumor. In every case the primary underlying cause of death was old thrombosis of the portal vein. The immediate causes of death included gangrene or infarction of the jejunum in two cases and generalized thrombosis of veins with pulmonary embolism, postoperative hemorrhage and localized peritonitis with ileus in one case each. The quantity of the ascitic fluid found at necropsy in these cases varied from 1,500 to 10,000 cc. Evidence of extrahepatic collateral circulation was generally present and in four cases gastric or esophageal varices were noted. Two of these patients gave a history of having bled from the upper part of the gastrointestinal tract but none of them experienced a terminal or fatal hemorrhage from esophageal varices.

Pathologic Findings. Hepatopetal or accessory portal veins, which shunted blood around the zone of portal obstruction to enter the liver, were prominent in the hepatoduodenal ligament in only two cases. In three cases neither the gross description nor the histologic sections revealed any marked development of these veins. Adequate sections including the hepatoduodenal ligament as well as the portal vein were lost in one case. In addition to ascites, hydrothorax was present in two cases.

The spleen was usually enlarged. The weight of the five spleens in this group was 35, 820, 1,480, 2,005 and 2,270 gm., respectively, with a mean weight of 1,322 gm. The appearance of the smallest spleen suggested that infarction had occurred many years previously. The liver was usually smaller than normal; the weight of the liver in the three cases in which it was recorded was 1,200, 1,382 and 1,560 gm., respectively, with a mean weight of 1,381 gm. In a fourth case the record stated that the liver was decreased in size.

Histologic examination of the portal vein revealed that this structure had been largely replaced by numerous smaller venous channels consisting largely of connective tissue lined with endothelium. It was difficult in many of these cases to delineate the original wall of the vein in routine sections stained with hematoxylin and eosin because of atrophy of the muscularis with fibrosis of the wall. With the help of the elastic-van Gieson stain, however, the remnants of the original wall of the portal vein could be identified in all cases, even when the muscularis was completely replaced by fibrous tissue, by finding remnants of the fragmented elastica interna and other elastic laminas. The lesions were interpreted as old organized and canalized thrombi

although the original thrombi were completely replaced by fibrous tissue and new vascular channels. In general, the new vascular channels within the lumen of the previously occluded vein and the new channels in the surrounding connective tissue of the hepatoduodenal ligament were not as large or as numerous in these cases as in the cases in which ascites had not occurred. Some of these new channels were obliterated also by old and recent thrombi and others revealed evidence of intimal fibrosis. The splenic vein also was frequently occluded by a well organized and well canalized thrombus but the mesenteric vein when involved was usually occluded by a recent thrombus.

Histologic study of the liver revealed mild to moderate chronic passive congestion in three cases, increased pigmentation and atrophy of hepatic cells, particularly in the central portions of the lobules in three cases, mild to moderate fatty change in three cases and periportal fibrosis in two cases. An increase in periportal lymphocytes and focal degeneration of liver cells were each observed in two cases.

Sections of the spleen were available for study in four cases. All but one revealed dilated sinuses and fibrosis of the pulp such as are observed in so-called Banti's disease. The single spleen which did not have this appearance was small and atrophied and weighed only 35 gm. In this spleen there was severe atrophy of both pulp and malpighian bodies with fibrous septa, arteries and arterioles and veins all in close apposition.

Inasmuch as renal lesions may play a role in the production of the ascites, all available sections of the kidneys were examined. Moderate endothelial proliferation in the glomerular tufts (glomerulitis) occurred in one case but this proliferation was not sufficient to permit a diagnosis of glomerulonephritis. Metastatic calcification of the tubular epithelium and calcification of casts were observed in one case.

Since hormones of the adrenal cortex may participate in the experimental production of ascites, all available sections of the adrenal glands were examined. The only noteworthy lesion was infarction of one-half of the right adrenal gland in one case.

COMMENT

Attempts to produce ascites in experimental animals by obstruction of the portal vein alone have for the most part been unsuccessful.[4–10] For this reason our cases of long-standing portal obstruction with ascites were scrutinized carefully for other lesions which might have a role in the production of the ascites. The clinical conditions which are known to lead to ascites, such as cirrhosis of the liver, congestive heart failure, chronic glomerulonephritis, mediastinal vena caval compression, carcinomatosis, tuberculous peritonitis, Meigs' syndrome and myxedema, were excluded by the method of selecting the cases.

Uncomplicated occlusion of the portal vein in man is not a common cause of ascites. In Cabot's[11] study of 2,217 cases of ascites at necropsy, cardiac disease, neoplastic involvement of the peritoneum, renal disease and cirrhosis of the liver were the most common conditions resulting in ascites. Only one case of thrombosis of the portal vein was found in his group.

Clinical studies of the incidence of ascites from occlusion of the portal vein are not numerous. Transient ascites occurred in four of eight cases of extrahepatic portal obstruction reported by Ratnoff, Conley and Berthrong[12] and in each instance the occurrence of ascites was preceded by massive gastrointestinal hemorrhage. Systematic studies at necropsy of the incidence of ascites associated with chronic occlusion of the portal vein are notably few. Klemperer[13] reviewed twenty-two cases of cavernomatous transformation of the portal vein and found ascites in six. Simonds[14] reviewed ninety-four cases of chronic occlusion of the portal vein and found ascites recorded in fifty-five of seventy-eight cases. In neither study does it appear that any attempt was made to exclude cases in which other lesions that could produce ascites were present. We were able to find in the literature reports of only seventeen cases in which at postmortem examination no cause for ascites was reported except chronic occlusion of the portal vein.[13,15–30] So far as we could ascertain, these cases are entirely comparable to the cases of occlusion of the portal vein with ascites in our series.

The present study indicates that in the majority of cases uncomplicated chronic portal occlusion does not result in ascites. According to our findings there are in the entire postmortem material at the Mayo Clinic only five cases of chronic occlusion of the portal vein in which ascites can be attributed solely to this lesion. On the other hand, occlusion of the portal vein may well have been an important or even a determin-

ing factor in the pathogenesis of the ascites in other cases excluded from this series because of the co-existence of other possible causes of ascites.

Perhaps of greater significance than its rarity is the fact that ascites due to occlusion of the portal vein does occur. This fact emphasizes the role of portal hypertension *per se* as an important contributing factor in the pathogenesis of ascites, particularly that of patients with cirrhosis of the liver, in whom this role has been minimized in recent years because of the failure to produce ascites in man and in experimental animals[1,4–8,31–33] by occlusion of the portal vein. It should be noted, however, that not all such attempts in animals have met with failure since Kunkel and Eisenmenger[34] produced mild transient ascites in 69 per cent of a series of rats by partially constricting the portal vein. Bolton[35] produced ascites in cats by the same method. Although ascites is more likely to occur when venous hypertension exists throughout the entire portal system (that is, in cirrhosis of the liver) than when only the extrahepatic portion of the portal system is involved, the occurrence of cases such as those herein reported indicates that portal hypertension need not necessarily exist within the liver in order to operate as an important factor in the production of ascites.

Hypoproteinemia, which is known to be an important factor in the production of ascites, could not be evaluated in our series since the concentration of protein in the blood was determined in only one case. In this patient (Case VI) the serum total protein and the serum albumin on one occasion measured 6.2 and 3.4 gm. per 100 cc., respectively, values only slightly less than normal. Considering the fact that frequent abdominal paracentesis with removal of large amounts of fluid which contained protein had been carried out in a period of two years, these values are surprisingly near to normal. The absence of peripheral edema and the presence of marked ascites in all our cases during the terminal illnesses make it seem unlikely that hypoproteinemia alone was responsible for the production of the ascites. The value for serum protein was not ascertained in any of the cases of ascites due to occlusion of portal vein found in the literature. That hypoproteinemia may have been a significant factor in the causation of the ascites in at least some of these cases is suggested by the frequency with which ascites appeared shortly after the occurrence of severe gastrointestinal hemorrhages.[15,16,21,24,25] On the other hand, in at least six cases ascites was the initial symptom and the patients had not had any previous illness which might have brought about reduction of plasma protein levels.

Comparison of the group of cases with ascites to the group without ascites shows both similarities and differences. The similar features included the sex incidence, the incidence of gastric and esophageal varices and the histologic appearance of the spleen and the liver. Differences between the two groups include the lower age incidence, the more frequent occurrence of well developed accessory portal veins (hepatopetal circulation) and a lesser degree of enlargement of the spleen and atrophy of the liver in patients without ascites. Because of the small number of cases in the two groups no great significance can be ascribed to these differences. The lower mean age of patients without ascites may possibly account for their more extensively developed collateral circulation. Vascular adaptation by opening up of collateral channels would be expected to be more vigorous in the young.

Pick[2] made a useful distinction between two types of collateral circulation which may develop in cases of obstruction of the portal vein: the hepatopetal and the hepatofugal. When the circulation through the liver itself is unimpeded and the obstruction is limited to the portal vein, the hepatopetal circulation may compensate more or less completely by shunting the blood around the obstruction to the liver. This hepatopetal circulation is accomplished through numerous normal or anomalous channels which enlarge to accommodate the increased flow through them. Most important and constant of these channels are the accessory portal veins of Sappey, which consist of small vessels which arise in the folds of the peritoneum connected with the liver or which come from the stomach and pass either into the stem of the portal vein or directly into the substance of the liver. In contradistinction to these channels the hepatofugal circulation shunts much of the blood from the abdominal viscera around the liver and to the systemic venous system. The best known and most often observed of these channels are the esophageal and hemorrhoidal veins.

Simonds[14] stated that the presence or absence of ascites depends on the adequacy of the collateral circulation. He collected ninety-four cases of occlusion of the portal vein from the literature

and divided them into two groups. In the cases of the first group the vein was reduced to a fibrous cord with relatively slight canalization. In the cases of the second group the portal vein was replaced by an elongated mass of spongy, cavernous tissue in which traces of the wall of the vein were usually but not always discernible. This alteration occurred at any place between the junction of the splenic and mesenteric vein and the hilus of the liver or even extended deeply into the liver. Ascites occurred in 85 per cent of the cases of the first group and in only 48 per cent of the cases in the second group.

Inasmuch as Simonds[14] did not exclude cases of cirrhosis of the liver (cirrhosis was present in seven cases in the first group), congestive heart failure or other clinical conditions associated with ascites, his data are not strictly comparable with ours. However, in nine of our ten cases in which there was no ascites the hepatopetal circulation (accessory portal veins) was well developed. These cases were similar to the cases in Simonds' second group. The accessory portal veins were well developed in only two of our five cases of ascites. Our studies therefore tend to support Simonds' observation that ascites is not likely to develop when the hepatopetal circulation is well developed.

SUMMARY AND CONCLUSIONS

A review was made of 215 cases of occlusion of the portal vein. From these we have selected for consideration fifteen cases of chronic occlusion of the portal vein which was not complicated by congestive heart failure, peritoneal carcinomatosis, renal disease, cirrhosis of the liver or any other lesion that might by itself be responsible for ascites. In ten of these cases no ascites was present, in five ascites was present and was of long standing. Clinical and pathologic evidence of portal hypertension was found in every instance.

This study revealed that in the majority of cases portal hypertension due to chronic extrahepatic obstruction of the portal vein is not associated with ascites. Contrary to the results of most studies on animals, however, this study indicates that portal hypertension secondary to chronic obstruction of the portal vein may result in ascites. This fact is confirmed by the finding in the literature of other similar cases in which ascites was attributable to occlusion of the portal vein alone. The results of this study, then, emphasize portal hypertension *per se* as an important contributing factor in the pathogenesis of ascites, even in the absence of hypertension of the intrahepatic portal system.

Comparison of the two groups of cases, those in which ascites was present and those in which it was absent, revealed that in the group without ascites the mean age was lower, the occurrence of better developed accessory portal veins (hepatopetal circulation) was more frequent, and the degrees of enlargement of the spleen and of atrophy of the liver were less. Although no great significance can be ascribed to these differences because of the small number of cases in the two groups, these findings suggest that inadequate development of the hepatopetal collateral circulation may be a determining factor in the development of ascites in some cases of chronic occlusion of the portal vein.

REFERENCES

1. Hyatt, R. E. and Smith, J. R. The mechanism of ascites: a physiologic appraisal. *Am. J. Med.*, 16: 434, 1954.
2. Pick, L. Über totale hämangiomatöse Obliteration des Pfortaderstammes und über hepatopetale Kollateralbahnen. *Arch. path. Anat.*, 197: 490, 1909.
3. Weir, J. F. and Beaver, D. C. Diseases of the portal vein: a review of 127 instances. *Am. J. Digest. Dis.*, 1: 498, 1934–1935.
4. Volwiler, W., Grindlay, J. H. and Bollman, J. L. The relation of portal vein pressure to the formation of ascites—an experimental study. *Gastroenterology*, 14: 40, 1950.
5. Berman, J. K. and Hull, J. E. Experimental ascites—its production and control. *Surgery*, 32: 67, 1952.
6. Welch, C. S. Medical progress: portal hypertension. *New England J. Med.*, 243: 598, 1950.
7. Douglass, T. C., Mehn, W. H., Lounsbury, B. F., Swigert, L. L. and Tanturi, C. A. Attempts at the experimental production of portal hypertension. *Arch. Surg.*, 62: 785, 1951.
8. Schilling, J. A., McCoord, A. B., Clausen, S. W., Troup, S. B. and McKee, F. W. Experimental ascites: studies of electrolyte balance in dogs with partial and complete occlusion of the portal vein and of the vena cava above and below the liver. *J. Clin. Investigation*, 31: 702, 1952.
9. Milnes, R. I. Constriction of thoracic inferior vena cava in rabbits following two-stage portal ligation. *Proc. Soc. Exper. Biol. & Med.*, 76: 147, 1951.
10. Wiles, C. E., Jr., Schenk, W. G., Jr. and Lindenberg, J. The experimental production of portal hypertension. *Ann. Surg.*, 136: 811, 1952.
11. Cabot, R. C. The causes of ascites: a study of 5,000 cases. *Am. J. M. Sc.*, 143: 1, 1912.
12. Ratnoff, O. D., Conley, C. L. and Berthrong, M. The differentiation between extrahepatic and intrahepatic obstruction of the portal circulation: a clinical study of the "Banti syndrome." *Bull. Johns Hopkins Hosp.*, 87: 305, 1950.

13. Klemperer, P. Cavernomatous transformation of the portal vein: its relation to Banti's disease. *Arch. Path.*, 6: 353, 1928.
14. Simonds, J. P. Chronic occlusion of the portal vein. *Arch. Surg.*, 33: 397, 1936.
15. Botkin. Krankheitsgeschichte eines Falles einer Pfortaderthrombose. *Virchows Arch. f. path. Anat.*, 30: 449, 1864.
16. Leyden, E. 1. Aus der Königsberger medicinischen Klinik Fälle von Pfortaderthrombose. *Berl. klin. Wchnschr.*, 3: 129, 1866.
17. Balfour, G. W. and Stewart, T. G. Case of enlarged spleen complicated with ascites, both depending upon varicose dilatation and thrombosis of the portal vein. *Edinburgh M. J.*, 14: 589, 1869.
18. Oppolzer, O. Cited by Bormann.[20]
19. Pippow. Cited by Bormann.[20]
20. Bormann. Beiträge zur Thrombose des Pfortaderstammes. *Deutsches Arch. f. klin. Med.*, 59: 283, 1897.
21. Umber, F. Beitrage zur Pfortaderobliteration. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 7: 487, 1901.
22. Buday, K. Ueber die Sklerose der Pfortader. *Centralbl. f. allg. Path. u. path. Anat.*, 14: 161, 1903.
23. Schulz, O. and Müller, L. R. Klinische, physiologische und pathologisch-anatomische Untersuchungen an einem Fall von hochgradigem Ascites bei Pfortaderthrombose. *Deutsches Arch. f. klin. Med.*, 76: 544, 1903.
24. Goldmann, G. Zur Kasuistik der Milzvenen- und Pfortaderthrombose. *Deutsche med. Wchnschr.*, 2: 1542, 1913.
25. Gruber, G. B. Beiträge zur Pathologie der dauernden Pfortaderverstopfung. *Deutsches Arch. f. klin. Med.*, 122: 319, 1917.
26. Mennet, J. Die Bantische Krankheit und ihre Beziehungen zur Leberzirrhose. *Arch. path. Anat.*, 227: 266, 1920.
27. Eppinger, H. Die hepato-lienalen Erkrankungen (Pathologie der Wechselbeziehungen zwischen Milz, Leber und Knochenmark), p. 393. Berlin, 1920. Julius Springer.
28. Kuhr, P. Zur Kenntnis der Pfortaderobliteration. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 37: 177, 1923–1924.
29. Falkenberg, J. Beitrag zur Kenntnis der chronischen Pfortaderverlegungen. *Arch. path. Anat.*, 268: 769, 1928.
30. Fleischhauer, H. Über den chronischen Pfortaderverschluss. *Arch. path. Anat.*, 286: 747, 1932.
31. Madden, J. L., Loré, J. M., Jr., Gerold, F. P. and Ravid, J. M. The pathogenesis of ascites and a consideration of its treatment. *Surg., Gynec. & Obst.*, 99: 385, 1954.
32. Hyatt, R. E., Lawrence, G. H. and Smith, J. R. Observations on the origin of ascites from experimental hepatic congestion. *J. Lab. & Clin. Med.*, 45: 274, 1955.
33. Child, C. G. The portal circulation. *New England J. Med.*, 252: 837, 1955.
34. Kunkel, H. G. and Eisenmenger, W. J. Increased portal pressure and ascites in rats following ligation of the portal vein. *Proc. Soc. Exper. Biol. & Med.*, 71: 212, 1949.
35. Bolton, C. An experimental study of the pathology of cardiac dropsy, and its relation to that of local venous obstruction. *J. Path. & Bact.*, 14: 49, 1910.

Infectious Mononucleosis Hepatitis*

A Clinicopathologic Study

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Of all the different types of clinical involvement during the course of infectious mononucleosis (eyes, pharynx, lungs, lymph nodes, heart, central nervous system, bone marrow, spleen, liver) that of the liver producing acute diffuse hepatitis has received perhaps the closest attention in recent years. Many observers in studying the disease have found liver involvement clinically and by laboratory tests in from 55 to 100 per cent of their individual series.[3,10,12,13,16,21] For several years such writers have been of the opinion that because of this frequent involvement, and the often prolonged convalescence which might be related to the hepatitis, all patients with infectious mononucleosis should be treated with appropriate diet and rest until clinical and laboratory signs approached normal.[1,3,6,10,13,16] Several, in drawing attention to occasional cases of chronic or persistent hepatitis following the disease, have pointed out that in some instances permanent chronic liver damage may ensue. The majority of such studies have been based on clinical and laboratory evidence of hepatic disease; the specific histopathologic condition has been established by liver biopsy and postmortem examination.[2,5,9,14,15,22,25,29,39,42,44]

With the more widespread use of liver biopsy as a clinical tool it was believed that a study employing this means, together with the clinical and laboratory findings, might help to clarify important points which are still obscure. The present study was undertaken with the following objectives in mind: (1) to trace the clinical and histopathologic progress of the disease; (2) to determine the proportion of cases showing pathologic involvement of the liver; (3) to study the incidence and progress of chronic hepatitis and (4) to establish the histopathology of the liver in that group of cases clinically resembling infectious mononucleosis but exhibiting a non-diagnostic heterophile antibody titer. While a small series could not hope to give conclusive answers to all these questions, evidence might be obtained which would give a clearer concept of this type of hepatitis.

MATERIAL

Patients were selected from the wards for patients with upper respiratory infections, United States Army Hospital, Fort Knox, Kentucky, on the basis of clinical, physical and laboratory evidence of infectious mononucleosis. All patients accepted for study were required to have a heterophil antibody titer of at least 1:224, in most instances confirmed by guinea pig kidney and beef cell absorption studies. Selection was made on the basis of the original disease, and not because of signs of hepatic involvement primarily. Thus the cases presented herein represent almost all patients with infectious mononucleosis admitted to the hospital during the period of the study. Once the diagnosis was made, no patient was excluded. There were nineteen young men in apparent good health except for the acute illness. Three additional patients who clinically appeared to have infectious mononucleosis, with typical blood counts and abnormal lymphocytes but with non-diagnostic heterophil antibody titers, were also studied.

METHODS

Heterophil antibody determinations were repeated at frequent intervals, especially in those patients suspected to have the disease on clinical grounds but in whom non-diagnostic titers were obtained in the first test. Liver function studies included determinations of serum bilirubin, cephalin cholesterol flocculation, thymol turbidity and bromsulfalein retention, which were performed by the laboratory service using methods described in the Armed Forces Technical

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TABLE I*

PERTINENT DATA IN CASES OF INFECTIOUS MONONUCLEOSIS WITH DIAGNOSTIC HETEROPHIL ANTIBODY TITERS (GROUP I)

Case No.	Enlargement of Liver	Enlargement of Spleen	Angina	H.A.T.	G.P.	B.C.	BSP	Serum Bilirubin (mg. %)	C.F.	T.T.
1	1+	1+	0	7168	Pos.	Neg.	40	3.2	4+ 4+	8.0
2	0	0	1+	896	Pos.	Neg.	10	0.6	2+ 4+	11.0
3	1+	1+	1+	1792	Pos.	Neg.	18	1.0	4+ 4+	4.5
4	0	0	1+	3584	Pos.	Neg.	18	0.6	2+ 2+	15
5	0	0	1+	7168	Pos.	Neg.	28	1.5	4+ 4+	14
6	0	0	1+	448	Pos.	Neg.	18	1.0	3+ 4+	3.0
7	1+	0	1+	1792	N.D.	N.D.	8	0.8	1+ 2+	4.0
8	0	0	1+	1992	Pos.	Neg.	20	N.D.	3+ 4+	5.5
9	0	0	0	896	Pos.	Neg.	4	1.0	0 1+	11
10	0	1+	1+	7168	Pos.	Neg.	36	N.D.	4+ 4+	N.D.
11	0	1+	1+	1792	Pos.	Neg.	4	0.3	N.D.	N.D.
12	1+	1+	0	7168	Pos.	Neg.	68	3.7	4+ 4+	15
13	0	1+	1+	1792	Pos.	Neg.	20	1.3	4+ 4+	3
14	0	1+	1+	1792	Pos.	Neg.	21	0.4	2+ 3+	5
15	0	1+	1+	224	Pos.	Neg.	11	0.7	2+ 4+	12
16	0	1+	1+	224	Pos.	Neg.	5	0.6	N.D.	5
17	1+	3+	1+	1792	Pos.	Neg.	7	0.7	2+ 3+	5
18	0	0	0	3586	Pos.	Neg.	27	2.0	4+ 4+	10
19	2+	1+	0	7168	Pos.	Neg.	5	1.2	2+ 4+	11

Abbreviations: H.A.T.: Heterophil antibody titer. G.P.: Guinea pig kidney absorption (pos. indicates little or no absorption). B.C.: beef cell absorption (neg. indicates complete absorption). BSP: Bromsulfaelin retention % (1 mg./Kilo in 45 min.; over 5% retention abnormal). C.F.: Cephalin flocculation, 2–4+ pos. T.T.: Thymol turbidity, higher than 8 abnormal. N.D.: not determined.

Manual No. 8-227. Patients were checked daily as to physical findings and general complaints. Liver biopsy specimens were taken in all cases studied (total of twenty-two, in whom there were twenty-nine biopsies). Since it was not judged desirable to take serial biopsies in every instance, specimens were obtained at different intervals during the disease in all the clinically milder cases (thirteen patients), and repeat biopsy specimens were taken in six cases clinically judged more severe. In one of these patients three biopsy specimens were taken. The three patients with clinical manifestations of infectious mononucleosis but with non-diagnostic heterophil titers were all subjected to histopathologic examination of the liver fairly early in the course of the disease. (two to five weeks). There were no complications and an adequate specimen was obtained in all instances.

CLINICAL DATA

The clinical and chief laboratory findings are summarized in Tables I and II, in which the data

TABLE II*

DATA IN CASES RESEMBLING INFECTIOUS MONONUCLEOSIS WITH NON-DIAGNOSTIC HETEROPHIL ANTIBODY TITERS (GROUP II)

Case No.	Enlargement of Liver	Enlargement of Spleen	Angina	H.A.T.	G.P.	B.C.	BSP	Serum Bilirubin (mg. %)	C.F.	T.T.
1	0	0	1+	Neg.	Neg.	Neg.	16	0.6	2+ 3+	3.0
2	0	0	1+	56	N.D.	N.D.	15	1.2	2+ 3+	0.5
3	0	0	1+	28	N.D.	N.D.	28	1.2	1+ 2+	3.0

* See footnote to Table 1, p. 27.

for liver function tests and heterophil antibody determinations represent the maximal results obtained in the individual cases. Table 1 indicates the findings in nineteen patients with diagnostic heterophil antibody titers (hereinafter referred to as group 1) and Table II gives the equivalent data in three patients with negative or non-diagnostic antibody titers (to be referred to as group II). Both groups show similar findings except for heterophil levels. Since all patients had fever, enlarged lymph nodes and lymphocytosis with abnormal lymphocytes, these features are not recorded in the tables.

As noted by others[6,8,42,50] there was a high incidence of fever, angina and lymphadenopathy. The liver and spleen were less constantly involved. Lymphocytosis and abnormal lymphocytes, the latter usually in large numbers, were noted in every instance. Absorption tests performed in group 1 in all but Case 7, in which the titer was 1:1792, showed incomplete absorption by guinea pig kidney and complete absorption by beef cells. Absorption tests were not performed in the patients comprising group II.

Tests for hepatic function showed abnormal values in every instance although the degree of abnormality was slight in several cases. Bromsulphalein retention was moderate to high in eighteen patients, the cephalin cholesterol flocculation test was positive in all but one patient tested (two not determined), thymol turbidity values were elevated in eight. Clinical jaundice was evident in only one instance (Case 1), although elevations of total serum bilirubin above 1.2 mg. per cent were found in five. In general, these findings correlate well with those of others[6,7,12,13,16,21,23] although thymol turbidity values have been more consistently elevated in other series.[10,13,41] It was believed that the cases in group 1 satisfied all recognized criteria for infectious mononucleosis, while those in group II lacked only diagnostic heterophil antibody levels. Tests for impaired hepatic function during the acute phase indicated mild to severe impairment in all cases except two in group 1 (Cases 11 and 16).

HISTOPATHOLOGIC STUDIES

The histopathology of the liver in infectious mononucleosis has been well delineated by post-mortem[2,14,15,22,29,44] and histopathologic[5,9,14,25,42] studies. The findings indicate that the abnormalities found take three main forms: portal exudates, consisting almost entirely of abnormal amounts of mononuclear cells; invasion of sinusoids by the same type of cells; and areas of scattered focal necrosis, filled with mononuclear cells. These latter may be in any portion of the lobule and are, in the experience of most, the least frequently seen. In the acute case, parenchymal cell regeneration may be active although large areas of necrosis such as those found in acute viral hepatitis have not been described. A typical section showing all three types of changes is illustrated in Figure 1.

Biopsy specimens in this series were for the most part taken in the early stages of the disease but several were staggered through the course of convalescence in an attempt to delineate the duration of pathologic change in the liver. The biopsy specimens were judged positive when two or more of the three main types of structural abnormality were noted. Six patients clinically judged more severe underwent removal of tissue

for biopsy again during convalescence. One of these patients, the only one to show persistent clinical activity, had three biopsies, and will be reported in detail. The pathologic findings in each specimen, with stage of disease (in weeks) in which biopsy specimens were obtained, are shown in Table III. Group I (positive heterophil) and group II (negative heterophil) are described separately. The experience of previous observers was borne out in that focal necrosis was noted in only eight cases of group I and one of group II. Portal and sinusoidal infiltrates were seen almost equally in both groups, and were present in almost all of the specimens yielding positive results.

TABLE III
LIVER BIOPSY SPECIMEN RESULTS

Case No.	Biopsy Number	Date	Week*	Portal Infiltrates	Sinusoidal Infiltrates	Focal Necrosis
			Group I			
1	1	12/2/53	5	+	+	+
	2	1/12/54	10	+	0	0
	3	5/7/54	28	+	+	0
2	1	2/12/54	3	+	+	+
	2	3/31/54	10	0	0	0
3	1	2/16/54	3	+	+	+
	2	4/20/54	12	0	0	0
4	1	2/24/54	4	+	+	+
	2	3/30/54	9	0	0	0
5	1	2/26/54	5	+	+	+
	2	3/30/54	9	+	0	0
6	1	12/4/53	4	+	+	+
	2	5/5/54	30	0	0	0
7	1	12/11/53	7	0	0	0
8	1	12/9/53	4	0	0	0
9	1	2/24/54	5	0	+	+
10	1	4/15/54	2	+	+	+
11	1	4/21/54	2	+	+	0
12	1	5/24/54	3	+	+	0
13	1	7/13/54	3	+	+	0
14	1	7/23/54	4	+	+	0
15	1	8/6/54	2	+	+	0
16	1	8/6/54	3	+	+	0
17	1	5/7/54	3	+	+	0
18	1	8/11/54	2	+	+	0
19	1	8/11/54	6	0	0	0
			Group II			
1	1	11/30/54	5	0	+	0
2	1	12/18/54	3	+	+	+
3	1	1/6/54	2	+	+	0

* Week of illness, dated from onset of symptoms.

Complete healing occurred in five of the six cases judged as being clinically severe; only one biopsy specimen gave a positive result after the fifth week, this from the patient with persistent hepatitis mentioned previously. Although all but two patients (Cases 11 and 16) showed laboratory evidence of hepatitis, biopsy specimens taken after this date, in which only one histopathologic examination was performed, showed no definite evidence of disease. Specimens in group II gave positive results in two instances (during the second and third weeks) while the third case yielded negative results (biopsy specimen taken in the fifth week).

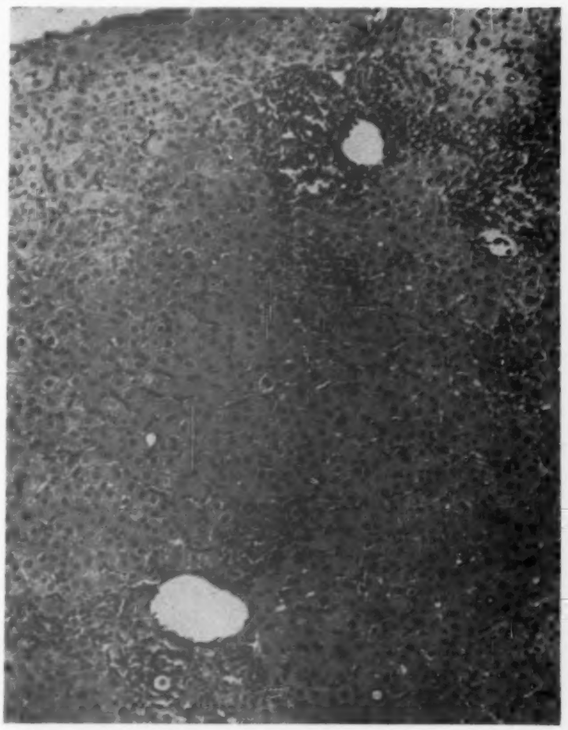

FIG. 1. Case 6. Biopsy at four weeks, showing periportal and sinusoidal mononuclear infiltrates, areas of focal necrosis and active regeneration of hepatic cells. Repeat biopsy at thirty weeks showed complete clearing.

PERSISTENT HEPATITIS

Only one instance of persistent clinical and pathologic hepatitis was observed in this series; this patient (Case 1) is reported in detail.

Case Report

A twenty year old white soldier was admitted to the United States Army Hospital, Fort Knox, Kentucky, October 28, 1953. He had been well until just prior to admission when generalized lymphadenopathy, slight scleral icterus, mild temperature elevation, vomiting and anorexia developed. The past history revealed

severe pneumonia and bilateral mastoidectomy in childhood. The patient did not consume alcohol in any form. His father was living and had had pulmonary tuberculosis which was now in the arrested stage; all other members of the family were well. On physical examination the liver was found to be enlarged and tender, 1 cm. below the right costal margin; the spleen was palpable 2 cm. below the left costal margin, and was firm and tender. The patient was acutely ill the first few days after admission, requiring parenteral fluids because of vomiting and anorexia. The liver and spleen both increased slightly in size at first but after one week the tip of the spleen was barely palpable, the liver receded and the patient began to eat well. On November 2, 1953, the total serum bilirubin was 3.2 mg. per cent, the cephalin flocculation test 4 plus, thymol turbidity 7.5 units and bromsulphalein retention 40 per cent. The heterophil antibody reaction was positive in 1:7168 dilution; absorption on guinea pig kidney showed reduction to 1:448 and beef cell absorption was complete. On November 30, 1953, the total serum bilirubin was 1.0 mg. per cent, the cephalin flocculation test 4 plus, thymol turbidity 10 units. Bromsulfalein retention was 5 per cent and the heterophil agglutination 1:896. By December 2nd the patient was asymptomatic and the physical examination was normal. A liver biopsy specimen taken on this date revealed small focal necrotic areas infiltrated with lymphocytes, lymphocytic infiltration in periportal areas as well as intralobular areas, with moderate numbers of segmental neutrophils throughout the section. The hepatic vessels were congested and red cells were noted within the sinusoids. Because of the histopathologic findings, and despite the fact that the patient appeared well, he was continued on the usual hepatitis regimen of high protein, high carbohydrate diet, with milk shakes, bed time feedings, supplementary vitamins and extra rest. On January 12, 1954, a second biopsy specimen was taken which showed only minimal periportal infiltrates. The patient was returned to duty on January 15, 1954, without symptoms or abnormal physical findings. Following discharge from the hospital he was able to work without difficulty but found that he did not have as much energy as previously. On April 23rd he noted onset of headache, anorexia, generalized aching and pain in the right upper abdominal quadrant. Outpatient studies showed the liver edge to be palpable but no splenic enlargement was found. The white blood cells numbered 7,800, with 46 per cent lymphocytes some of which were atypical. The total serum bilirubin was 0.6 mg. per cent, the cephalin flocculation test 2 plus, thymol turbidity 6 units, bromsulphalein retention 11 per cent and the heterophil agglutination test negative. A liver biopsy specimen taken on May 7th revealed changes almost identical with those seen in the first biopsy specimen of December 2, 1953. The usual hepatitis regimen was again instituted and symptomatically the patient did very well. The liver was no longer palpable; the patient ate well and was soon up and about. Blood studies showed a lymphocytosis of 69 per cent with many atypical forms but the heterophil antibody reaction remained negative on repeated tests. The serum bilirubin was within normal limits throughout hospitalization; the cephalin flocculation test became 4 plus, then returned to normal, as did the thymol turbidity and bromsulphalein retention by July 19th. The serum cholesterol, cholesterol esters and proteins also remained within normal limits during this hospitalization. The patient was sent on two weeks' sick leave and returned asymptomatic, with no lymphadenopathy and no enlargement of liver or spleen. Because of the recurrent nature of his illness and the active type of work performed in his company he was put on a temporary retired status for re-evaluation at the end of six months. Typical lesions noted on the first and third histopathologic examinations in this case are shown in Figure 2.

HEMOLYTIC ANEMIA

Hemolytic anemia as a complication of infectious mononucleosis has been noted in other reports.[4,25] In the present series one patient (Case 19) showed unequivocal evidence of a hemolytic process as evidenced by anemia, initial reticulocyte count of 13.7 per cent, elevated serum bilirubin on admission, and a direct positive, indirect negative Coombs' reaction. The heterophil antibody titer was 1:7168; there was an enlarged liver and spleen, and lymphocytosis with many atypical lymphocytes was present. A liver biopsy specimen taken on August 11, 1954, in the sixth week of disease, showed no evidence of hepatitis although there was evidence of accelerated hemolytic processes at this time. Given cortisone, the patient's blood picture improved rapidly and he could be discharged to duty approximately twelve weeks after admission. This case is not reported in detail but mentioned to illustrate the point that severe hepatitis does not necessarily occur concomitantly with the hemolytic anemia, as in Gloyne's well documented report.[25] The hepatitis in this patient was mild and subsided before bone marrow hyperplasia had cleared, showing that in this instance at least the two processes were separate, although undoubtedly of similar causation.

COMMENTS

Chronic or persistent hepatitis has rarely been noted as a sequel of infectious mononucleosis. Cohn and Lidman[13] stated that in one of their patients chronic hepatitis apparently developed,

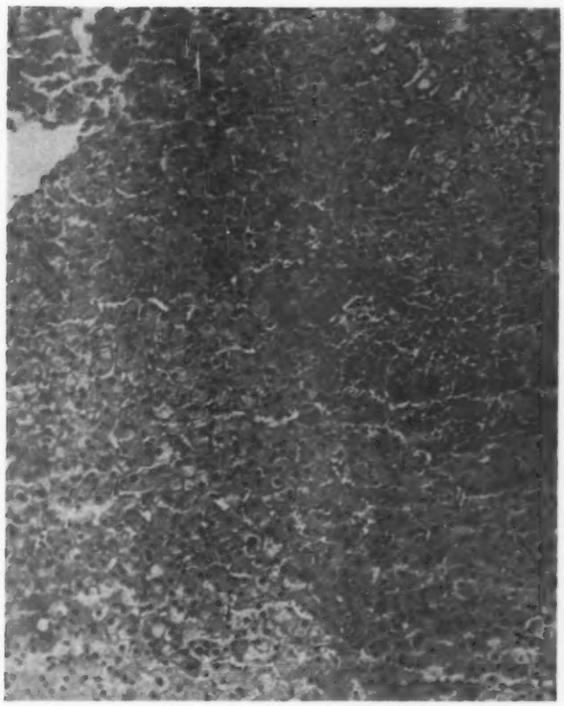

FIG. 2A. Case 1. At five weeks the specimen shows focal necrosis and sinusoidal infiltrates.

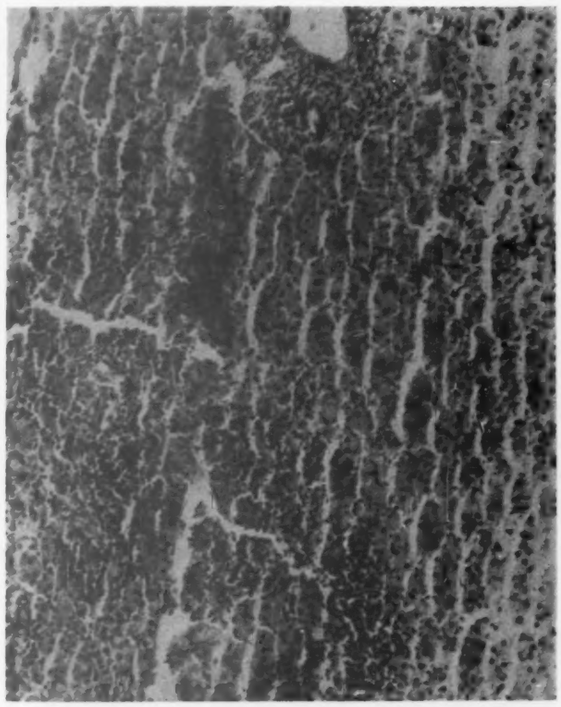

FIG. 2B. At twenty-eight weeks periportal, sinusoidal infiltrates with focal collections of inflammatory cells are still present, (separation of liver cords is artifact.)

as revealed by serial function tests; Bennett, Frankel, Bedinger and Baker[6] reported seven patients in whom there was evidence of chronicity or recurrence, one remaining symptomatic approximately two years after the onset of the disease. There is general agreement[7,10,13,16,28] that the usual course of hepatitis in infectious mononucleosis is two to six weeks, with rapid return to normal. Jordan and Albright,[28] however, suggested that "as in infectious hepatitis, the possible relationship of hepatitis in infectious mononucleosis to the pathogenesis of cirrhosis must now be considered." Leibowitz and Brody[31] reported a case in which they believed that the transition of this type of hepatitis to cirrhosis was demonstrated but the patient had a history of alcoholism and serial biopsies were not obtained throughout the course. Certainly such a possibility must be considered, along with other types of injury to the liver as a cause of cirrhosis. Continued severe inflammation of the liver with even small areas of focal necrosis, as in the present case, might well cause disruption of the reticulum framework of the lobule (or plate) and eventual deposition of fibrous tissue. Certainly with this as a basis other unrelated insults might cause further progression to severe fibrosis and cirrhosis, although in our case there is no evidence, after twenty-eight weeks, that these chronic changes have occurred. Further observation and study of this type of patient will be necessary to establish the role of infectious mononucleosis in causing permanent damage to the liver.

The criteria for the diagnosis of infectious mononucleosis have long been disputed. Due to the possibility of confusion with infectious (viral) hepatitis, it has been our practice to classify cases of hepatitis with a non-diagnostic heterophil antibody titer as non-specific or viral hepatitis despite any clinical similarity to infectious mononucleosis. We have been curious, however, to discover what structural changes histopathologic examination of the liver might reveal in such cases. Group II of this series consists of three cases in this category which were discovered during the period of study. Liver biopsy specimens in two of these patients, taken during the second and third weeks of the disease, showed changes indistinguishable from the positive specimens in group I. The third case showed only mild periportal infiltrates (biopsy specimen was taken in the fifth week of his disease). While the type of reaction seen in

infectious mononucleosis is very similar to that found in early viral hepatitis, the clinical courses in these three patients closely resembled those of group I in all respects. This may therefore be another bit of presumptive evidence to show that a small minority of patients with infectious mononucleosis do not have diagnostic heterophil antibody titers. More histopathologic and clinical studies in this type of case may serve to reinforce this evidence.

As stated earlier, many observers have noted evidence of acute hepatitis in infectious mononucleosis. Leibowitz, in an excellent monograph on the subject,[32] believes that evidence of hepatitis should probably be required as another criterion of infectious mononucleosis. In two of our patients (Cases 11 and 16) laboratory and clinical tests did not indicate the presence of hepatitis, although liver specimens showed marked periportal and sinusoidal infiltrates. Conversely, three patients (Cases 7, 8 and 19) in whom tissue was removed for biopsy at seven, four and six weeks, respectively, gave laboratory results indicative of hepatitis, and two had enlarged and tender livers. These were all patients in whom single biopsy specimens were taken and two were at the stage (later than five weeks) when all biopsy specimens, except that of the patient with persistent hepatitis, were found to be negative. It may be inferred, therefore, that in at least these two instances earlier biopsy specimens might have yielded positive results. It also would appear that in the great majority of patients the pathologic changes in the liver subside almost as quickly as laboratory and clinical evidence of hepatic disease. That this may not be true of all such hepatic involvement is demonstrated by Case 1, in which the liver biopsy specimen showed all three types of disease during a period in which the patient was clinically well and hepatic function tests had returned to normal. The correlation between histopathologic results and clinical and laboratory evidence of hepatitis is good in the majority of cases, however.

The results of our present series would indicate that in all but exceptional instances of persistent hepatitis, biopsy evidence of hepatitis subsides after the fifth week. All but one case in both groups I and II returned to normal clinically and by laboratory tests within this interval. This is in agreement with other observers who found that hepatitis in infectious mononucleosis subsides in two to six weeks. That all cases showed hepatitis by clinical, laboratory or histopathologic studies, and most cases by all types of evidence, is again good proof that patients with this disease should be treated for hepatic involvement by appropriate dietary and rest regimens. While such treatment did not avert persistent hepatitis in one of our patients, it may have materially advanced recovery in others with severe involvement.

SUMMARY

1. Twenty-two young men with clinical manifestations of infectious mononucleosis were studied by liver function tests and liver biopsy in an attempt to clarify aspects of hepatitis in this disease.

2. Function tests and/or biopsy indicated hepatic involvement in all cases, biopsy specimens showing return to normal in all but one instance within five weeks.

3. One case of persistent hepatitis, studied by function tests and serial biopsies, showed continuation of the disease for approximately eight months, and is still being followed up.

4. In three of the twenty-two cases heterophil antibody determinations remained below diagnostic levels. All three had abnormal liver function tests and two biopsy specimens yielded positive findings despite lack of confirmation of the diagnosis by the Paul-Bunnell test.

5. The significance of these results in the light of previous studies by other observers is discussed.

REFERENCES

1. Abrams, H. L. Infectious mononucleosis with intense jaundice of long duration. *New England J. Med.*, 238: 295–297, 1948.
2. Allen, F. H. and Kellner, A. Infectious mononucleosis. An autopsy report. *Am. J. Path.*, 23: 463–477, 1947.
3. Angle, R. M. Hepatitis without jaundice in infectious mononucleosis. *Gastroenterology*, 12: 617–622, 1949.
4. Appelman, D. H. and Gordon, G. B. Acute hemolytic anemia complicating infectious mononucleosis: report of two cases. *Ann. Int. Med.*, 41: 371–376, 1954.
5. Bang, J. and Wanscher, O. The histopathology of the liver in infectious mononucleosis complicated by jaundice, investigated by aspiration biopsy. *Acta med. Scandinav.*, 120: 437–466, 1945.
6. Bennett, H. D., Frankel, J. J., Bedinger, P. and Baker, L. A. Infectious mononucleosis with hepatitis. *Arch. Int. Med.*, 86: 391–401, 1950.
7. Berk, J. E., Shay, H., Ritter, J. A. and Siplet, H. Infectious mononucleosis and infectious hepatitis:

studies bearing on certain resemblances and differences. *Gastroenterology*, 11: 658–671, 1948.

8. Bernstein, A. Infectious mononucleosis. *Medicine*, 19: 85–159, 1940.
9. Bertrand, L. The liver in infectious mononucleosis. *Presse méd.*, 81: 1218–1220, 1949.
10. Brown, J. W., Sims, J. L., White, E. and Clifford, J. E. Liver function during infectious mononucleosis. *Am. J. Med.*, 6: 321–328, 1949.
11. Carpenter, G., Kahler, J. and Reilly, E. B. Elevated titers of serum heterophil antibodies in three instances of monocytic leukemia. *Am. J. M. Sc.*, 220: 195–198, 1950.
12. Carter, A. B. and MacLagan, N. F. Some observations on liver function tests in diseases not primarily hepatic. *Brit. M. J.*, 2: 80–82, 1946.
13. Cohn, C. and Lidman, B. I. Hepatitis without jaundice in infectious mononucleosis. *J. Clin. Investigation*, 25: 145–151, 1946.
14. Custer, R. P. and Smith, E. B. The pathology of infectious mononucleosis. *Blood*, 3: 830–857, 1948.
15. Davis, J. S., MacFee, W., Wright, M. and Allyn, R. Rupture of spleen in infectious mononucleosis. *Lancet*, 2: 72–73, 1945.
16. DeMarsh, Q. B. and Alt, H. L. Hepatitis without jaundice in infectious mononucleosis. *Arch. Int. Med.*, 80: 257–264, 1947.
17. Eaton, M. D., Murphy, W. D. and Hanford, V. L. Heterogenetic antibodies in acute hepatitis. *J. Exper. Med.*, 79: 539–557, 1944.
18. Evans, A. A. Experimental attempts to transmit infectious mononucleosis to man. *Yale J. Biol. & Med.*, 20: 19–26, 1947.
19. Evans, A. S. Further experimental attempts to transmit infectious mononucleosis to man. *J. Clin. Investigation*, 29: 508–512, 1950.
20. Evans, A. S. and Robinton, E. D. An epidemiologic study of infectious mononucleosis in a New England college. *New England J. Med.*, 242: 492–496, 1950.
21. Evans, A. S. Liver involvement in infectious mononucleosis. *J. Clin. Investigation*, 27: 106–110, 1948.
22. Fisher, J. H. Visceral lesions of acute infectious mononucleosis. A report of two cases with fatal spontaneous rupture of the spleen. *Am. J. Path.*, 22: 651–652, 1946.
23. Gall, E. A. Serum phosphatase and other tests of liver function in infectious mononucleosis. *Am. J. Clin. Path.*, 17: 529–533, 1947.
24. Gardner, H. T. and Paul, J. R. Infectious mononucleosis at the New Haven Hospital, 1921–1946. *Yale J. Biol. & Med.*, 19: 839–853, 1947.
25. Gloyne, H. F. Infectious mononucleosis. Report of an unusual case with hepatitis studied by serial liver biopsies and complicated by hemolytic anemia. *Am. Pract.*, 3: 628–632, 1949.
26. Goldman, R., Fishkin, B. G. and Peterson, E. T. The value of the heterophile antibody reaction in the lymphomatous diseases. *J. Lab. & Clin. Med.*, 35: 681–687, 1950.
27. Isaacs, R. Chronic infectious mononucleosis. *Blood*, 3: 858–861, 1948.
28. Jordan, W. S., Jr. and Albright, R. W. Liver function tests in infectious mononucleosis. *J. Lab. & Clin. Med.*, 35: 688–698, 1950.
29. Kass, E. H. and Robbins, S. L. Severe hepatitis in infectious mononucleosis. *Arch. Path.*, 50: 644–653, 1950.
30. Kaufman, R. E. Heterophile antibody reaction in infectious mononucleosis. *Ann. Int. Med.*, 21: 230–251, 1944.
31. Leibowitz, S. and Brody, H. Cirrhosis of the liver following infectious mononucleosis. *Am. J. Med.*, 8: 675–685, 1950.
32. Leibowitz, S. Infectious mononucleosis. In: Modern Medical Monographs. New York, 1954. Grune & Stratton.
33. Leibowitz, S. Heterophile antibody in normal adults and in patients with virus hepatitis. *Am. J. Clin. Path.*, 2: 201–211, 1951.
34. Litwins, J. and Leibowitz, S. Abnormal lymphocytes (virocytes) in virus diseases other than infectious mononucleosis. *Acta haemat.*, 5: 223–231, 1951.
35. Peterson, R. E. Hepatic dysfunction in infectious mononucleosis, with review of the literature. *J. Lab. & Clin. Med.*, 33: 1258–1270, 1948.
36. Read, J. T. and Helwig, F. C. Infectious mononucleosis. *Arch. Int. Med.*, 75: 376–380, 1945.
37. Schultz, A. L. and Hall, W. H. Clinical observations in 100 cases of infectious mononucleosis and the results of treatment with penicillin and aureomycin. *Ann. Int. Med.*, 36: 1498–1511, 1952.
38. Schultz, L. E. Heterophile antibody titer in diseases other than infectious mononucleosis. *Arch. Int. Med.*, 81: 328–333, 1948.
39. Smetana, H. F., Keller, T. C. and Dubin, I. N. Histologic criteria for the differential diagnosis of liver diseases in needle biopsies. *Rev. Gastroenterol.*, 20: 227–244, 1953.
40. Smetana, H. F. The histologic diagnosis of viral hepatitis by needle biopsy. *Gastroenterology*, 26: 612–623, 1954.
41. Sterling, K. The serum proteins in infectious mononucleosis. Electrophoretic studies. *J. Clin. Investigation*, 28: 1057–1066, 1949.
42. van Beek, C. and Haex, A. J. C. Aspiration-biopsy of the liver in mononucleosis infectiosa and Bernier-Boeck-Schaumman's disease. *Acta med. Scandinav.*, 113: 125–134, 1943.
43. Wechsler, H. F., Rosenblum, A. H. and Sills, C. T. Infectious mononucleosis; report of an epidemic in an Army Post. *Ann. Int. Med.*, 25: 113–265, 1946.
44. Ziegler, E. E. Infectious mononucleosis. Report of a fatal case with autopsy. *Arch. Path.*, 37: 196–201, 1944.

Essential Familial Hypercholesterolemia and Xanthomatosis*

Follow-up Study of Twelve Danish Families

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DURING the years 1941 to 1943 Kornerup examined several members of fourteen Danish families in whom essential hypercholesterolemia and xanthomatosis occurred as an inherited disorder. According to Kornerup, hypercholesterolemia is transmitted as a dominant trait, affecting both sexes with equal frequency. The serum cholesterol seems to be constantly elevated from childhood. Cutaneous and tendinous xanthomas are encountered in about half the patients with this disease, in some of the cases manifesting itself exclusively as palpebral xanthelasma. Xanthomas occur mainly in patients with markedly increased serum cholesterol (400 to 450 mg. per cent) whereas those with a moderately elevated serum level (325 to 400 mg. per cent) usually do not display any signs. Arcus senilis is encountered in about one-third of all patients with hypercholesterolemia. The incidence of coronary sclerosis with angina pectoris and sudden cardiac death is higher in these families than in the general population.

Wilkinson et al., on the basis of a comprehensive family study, have advanced a new theory concerning the mode of transmission: (1) Hypercholesterolemia is transmitted as a dominant (gene pair Cc); (2) cutaneous and tendinous xanthoma represents the homozygous abnormal (CC); (3) a normal serum cholesterol represents the homozygous normal (cc). This type of inheritance they call incomplete dominance, "because the severity of the condition is less in the heterozygote than in the homozygote."

In the series studied by Wilkinson et al. xanthomatosis occurred in only a few subjects, who were not proved to be homozygotes. The best substantiation of the views of these investigators would be the demonstration of nothing but heterozygous (hypercholesterolemic) persons in the offspring (CC + cc → Cc, Cc, Cc — — —), but only one of the offspring was examined (who did exhibit hypercholesterolemia, it is true). Adlersberg et al. claim that in their series they found support for Wilkinson's theory that patients with xanthomatosis are homozygotes. However, the evidence is marred by the fact that some of the children of a man or woman supposed to be homozygous had normal serum cholesterol levels.

In 1954 we conducted a follow-up study of Kornerup's patients with essential familial hypercholesterolemia. This follow-up study includes members who had not been examined by Kornerup (in part because of the difficulty of tracing patients and the difficulties of transportation during the German occupation of Denmark), as well as the children of hypercholesterolemic patients born after Kornerup had concluded his study. The purpose of this follow-up study was to determine the course of the disease during the intervening eleven to thirteen years, particular attention being devoted to the serum cholesterol, the incidence and degree of xanthomatosis, and the occurrence and prognostic significance of angina pectoris. By extending our study to include, as far as possible, all living members of these families we tried to obtain a numerical expression of the incidence of the various symptoms and signs of this hereditary disease in these families at a given juncture (1954). In an endeavor to shed some light on the mode of inheritance (so differently interpreted, as is evident from the publications of Kornerup, and Wilkinson and his associates), we in-

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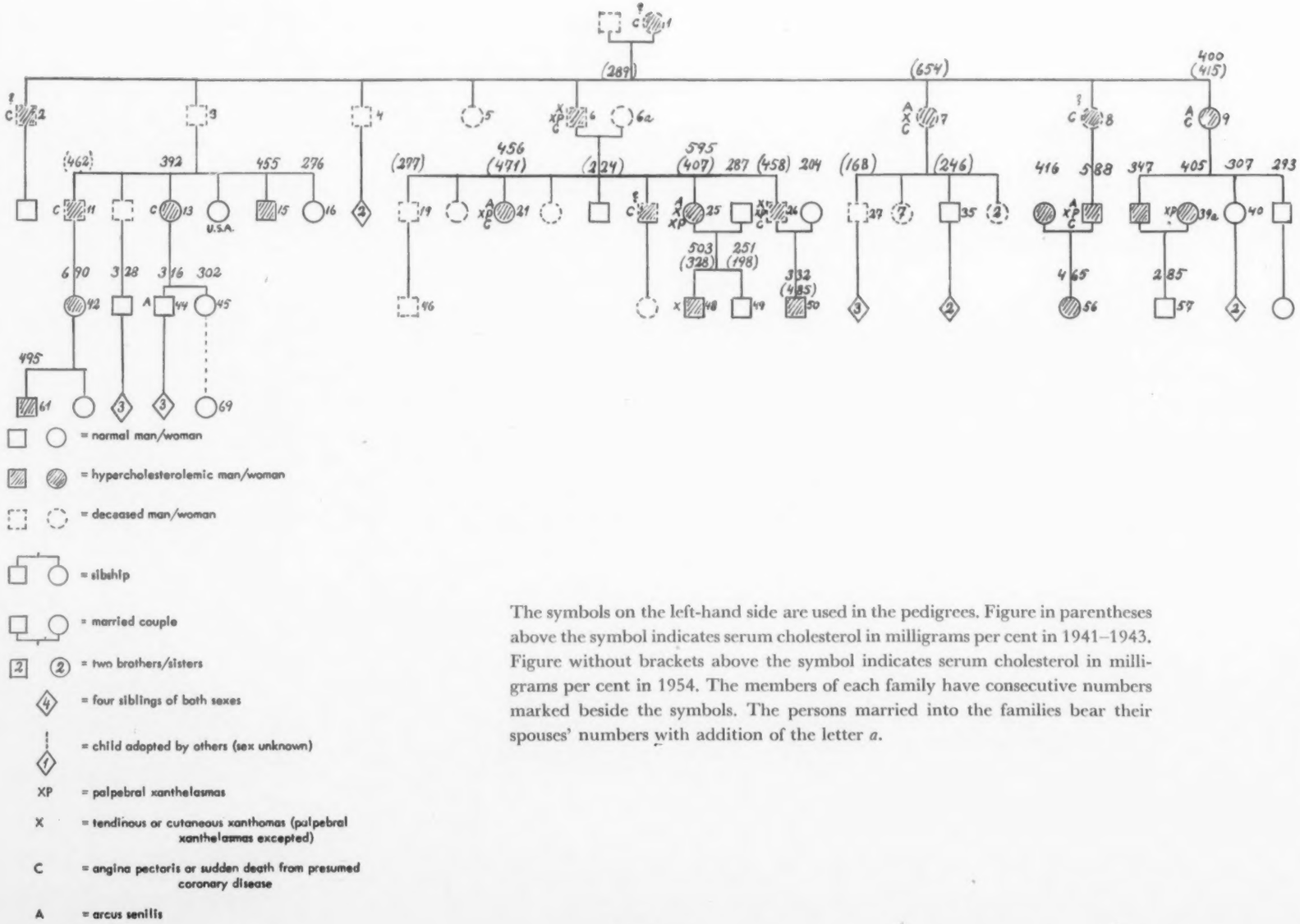
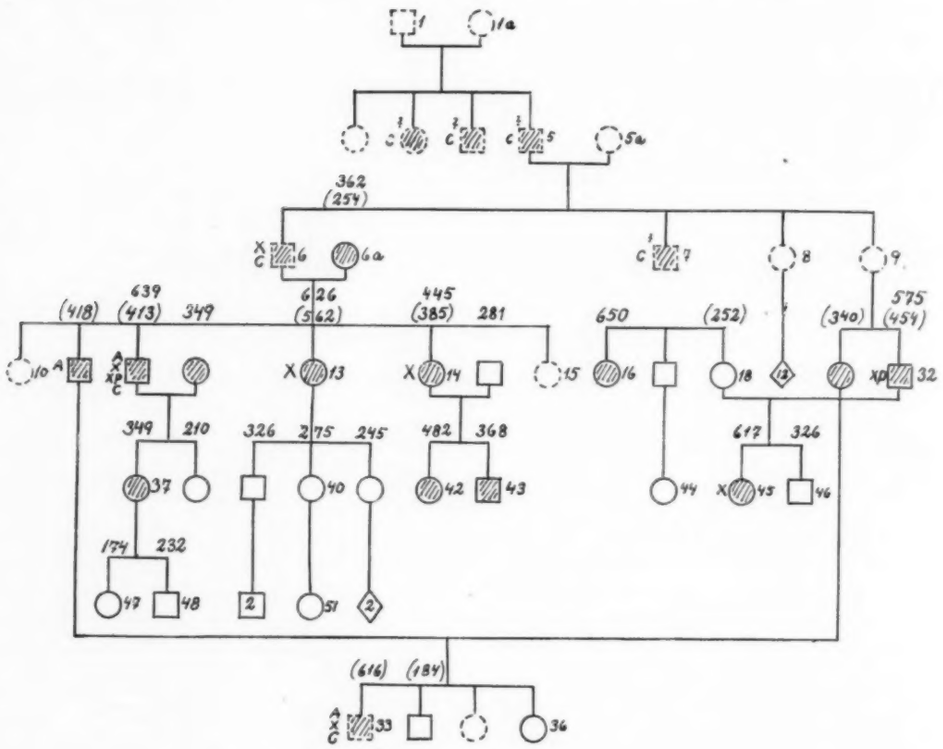


The symbols on the left-hand side are used in the pedigrees. Figure in parentheses above the symbol indicates serum cholesterol in milligrams per cent in 1941–1943. Figure without brackets above the symbol indicates serum cholesterol in milligrams per cent in 1954. The members of each family have consecutive numbers marked beside the symbols. The persons married into the families bear their spouses' numbers with addition of the letter *a*.

PEDIGREE I.



PEDIGREE II.

cluded many spouses of xanthomatous patients.

Our study comprises only twelve of Kornerup's fourteen families, excluding family IV, in which the disease became extinct even before Kornerup's study, and family XII in which there was only an isolated case and the remaining members were unknown. We tried to contact all the members of these twelve families apart from those individuals (and their children) who were not afflicted in 1941 to 1943. The subjects were seen in their homes. A few refused to see us, a few who lived abroad were not contacted, and a few could not be traced. About half of the subjects are living in Copenhagen and suburbs; the remainder are scattered all over Denmark. (Compare pedigrees.)

METHODS

In each individual case a careful history was taken with particular respect to cardiac symptoms, intermittent claudication, thyroid disorders and the approximate time at which xanthomas appeared. If the subject had been admitted to a hospital, any information believed to have a bearing on the disease was obtained from the hospital concerned. Such information was obtained in all cases of deaths occurring during hospitalization.

The clinical examination included inspection to detect arcus senilis, xanthelasma of the eyelids, goiter, inspection of the oral mucosa, auscultation of the heart, inspection of the skin, and inspection and palpation of tendons involving hands, elbows, infrapatellar regions, Achilles tendons and feet. Blood pressures were determined and electrocardiograms taken in all adults. Serum cholesterol was measured in all subjects over two years of age.

The determinations of serum cholesterol were carried out by the same laboratory technician, employing the analytic technic (Brun) that Kornerup used in 1941 to 1943. As in Kornerup's investigations, the upper normal limit of serum cholesterol was set at 340 mg. per cent in adults and at 325 mg. per cent in children. The subjects were not fasting at the time of sampling. Apart from the determinations of total cholesterol, no blood lipid determinations were undertaken. Kornerup's investigations, which included determinations of total lipid, justify our interpretation of the lipoidoses occurring in these families as instances of hypercholesterolemia. There is nothing to support the assumption that cases of essential hyperlipemia occurred in the present material.

RESULTS

In 1941 to 1943 Kornerup examined fifty-three persons with essential hypercholesterolemia derived from these twelve families. Of these

TABLE I

DATA ON SEVENTEEN PATIENTS WITH ESSENTIAL FAMILIAL HYPERCHOLESTEROLEMIA*

Family	No.	Sex	Age When Examined	Serum Cholesterol (mg. %)	Arcus Senilis	Palpebral Xanthelasma	Extrapalpebral Xanthomas†	Angina Pectoris (Duration in yr.)	Age at Death	Cause of Death	Autopsy Findings
I	26	♂	34	458	−	+	+	5	40	Coronary occlusion	Small, fresh myocardial infarcts; severe cholesterolosis of coronary arteries, moderate of aorta; myocardial fibrosis
I	7	♀	76	654	+	−	+	4	76	Coronary occlusion(?); sudden death	None
II	33	♂	13	616	+	−	+++	0	18	Coronary occlusion(?); sudden death	None
III	4	♂	50	416	−	+	+	½	60	Coronary occlusion	Cardiac rupture; cardiac myomalacia; myocardial fibrosis, severe arteriosclerosis of coronary arteries and aorta
VI	3	♀	40	421	−	+	+	8	40	Coronary occlusion(?); sudden death	None
VII	10	♂	55	475	+	+	+	4	56	Coronary occlusion(?); sudden death	None
VII	21	♂	30 40	418 500	−	+	++	4	41	Coronary occlusion	Coronary thrombosis; xanthomatosis of coronary arteries, aorta and pulmonary arteries; myocardial fibrosis
X	7	♂	44	513	+	−	+	2	47	Coronary occlusion	Cardiac myomalacia, infarct; sclerosis of aorta and coronary arteries
XI	20	♀	37	603	−	+	+	8	39	Coronary occlusion(?); sudden death	None
XIV	12	♀	54	686	−	+	+	3	55	Coronary occlusion(?)	None
III	2	♂	52	618	+	+	−	0	60	Cerebral hemorrhage	None
V	3	♀	61	505	−	−	+	0	62	Abdominal carcinoma	None
IX	2	♀	73	675	+	+	+	Many years	76	Cerebral hemorrhage	None
XI	5	♂	60 71	390 530	+	+	+	0	72	Carcinoma of prostate	None
XI	10	♀	49	596	+	+	++	?	59	Heart failure; arteriosclerotic heart disease(?)	None
XIII	6	♂	59	372	−	−	++	5	83	Pulmonary tuberculosis	None
XIII	2	♀	68	466	−	+	+	3	70	Purulent peritonitis	Empyema of gallbladder with perforation; diffuse peritonitis; mild atherosclerosis of aorta and coronary arteries

* These patients had been examined in 1941 to 1943 and had died before 1955: the first ten in the table from coronary occlusion (at an average age of 47.2 years) and the last seven from other diseases (at an average age of sixty-six years). Where two cholesterol values are given, the latter is derived from the follow-up in 1954 (shortly before death). The numbers represent the numbers of the patients in the twelve pedigrees.

† Small or scattered +; moderate ++; large or widespread +++.

fifteen had died before our study was begun, thirty-five were examined by us in 1954, and the remaining three refused to submit to a repeated examination.

Two of the re-examined patients died in 1954 to 1955, bringing the total number of deaths after Kornerup had concluded his study to seventeen. Table I gives the data on these seventeen subjects. As indicated in Table I, ten apparently died of coronary occlusion. In four of these cases the diagnosis was confirmed at autopsy; five died suddenly at home and were not autopsied,

TABLE II

FINDINGS IN THIRTY-FIVE PATIENTS WITH ESSENTIAL FAMILIAL HYPERCHOLESTEROLEMIA EXAMINED IN 1941 TO 1943 AND FOLLOWED UP IN 1954

	No. of Patients	Average Serum Cholesterol (mg. %)	Average Age (yr.)	No. with Latent Xanthomatosis	No. with Tendinous Xanthomatosis	No. with Extra-Palpebral Cutaneous Xanthomatosis	No. with Xanthelasma	No. with Cutaneous and/or Tendinous Xanthomatosis Including Xanthelasma	No. with Arcus Senilis	No. with Angina Pectoris	No. with Intermittent Claudication
1941–1943	35	438	37.3 (5–68)	18	12	4	4	17	12	2	1 (0?)
1954.....	35	534	49.0 (17–79)	10	19	5	15	25	17	8	4

one died in the hospital but autopsy was not permitted.

Nine of the ten patients had had angina pectoris for six months to eight years (average, 4.3 years). All ten of these subjects had extra-palpebral xanthomas of the skin or tendons, seven had xanthelasma palpebrarum and four had arcus senilis. The serum cholesterol ranged from 418 to 686 mg. per cent (averaging 526 mg. per cent) in 1941 to 1943 at which time the average age was 43.3 years (ranging from thirteen to seventy-six). The age at death was eighteen to seventy-six years (average, 47.2).

Seven died of other causes; autopsy was performed in only one. The others did not die in a hospital but the diagnoses are derived from hospital admissions shortly before death. Their average age was sixty-six years (ranging from forty-nine to seventy-three), their serum cholesterol concentrations varied from 372 to 675 mg. per cent (average, 517 mg. per cent) in 1941 to 1943.

Follow-up Series. A total of thirty-five subjects were re-examined by us in 1954, eleven to thirteen years after Kornerup's examination. Table II compares the main findings in this group of patients at the 1941 to 1943 examination and the 1954 follow-up study. It is evident that the average serum cholesterol had increased from 438 mg. per cent (320 to 686 mg. per cent) to 534 mg. per cent (332 to 855 mg. per cent) during the intervening period; that the cases of latent xanthomatosis (i.e., hypercholesterolemia without xanthomas) had been reduced from eighteen to ten; and that in twenty-five of the thirty-five patients manifest xanthomatosis had developed. Of the seventeen patients who had xanthomas in 1941 to 1943 the lesions had increased in number and size in all but one (family x_8) who exhibited a marked, spontaneous regression despite a considerable increase in serum cholesterol.

The ten patients who did not exhibit xanthomas, either at the original or follow-up examination, had an average serum cholesterol of 394 mg. per cent (320 to 485 mg. per cent) in 1941 to 1943 and 439 mg. per cent (332 to 590 mg. per cent) in 1954, whereas the twenty-five patients who presented xanthomas in 1954 had an average level of 456 mg. per cent (328 to 686 mg. per cent) in 1941 to 1943 and 572 mg. per cent (370 to 855 mg. per cent) in 1954. In 1954 the ten patients without xanthomas averaged 42.6 years in age (seventeen to seventy-nine) whereas the twenty-five subjects with xanthomas averaged 51.5 years (twenty-seven to seventy-eight). Thus the patients without xanthomas represent the younger age group. This possibly explains both the lower serum cholesterol and the fact that manifest xanthomas have not yet developed.

In Kornerup's entire series (those who had died as well as those who were followed up in 1954) we find that xanthoma tendinosum and/or tuberosum, including xanthelasma palpebrarum, occurred in 64 per cent in 1941 to 1943 and in

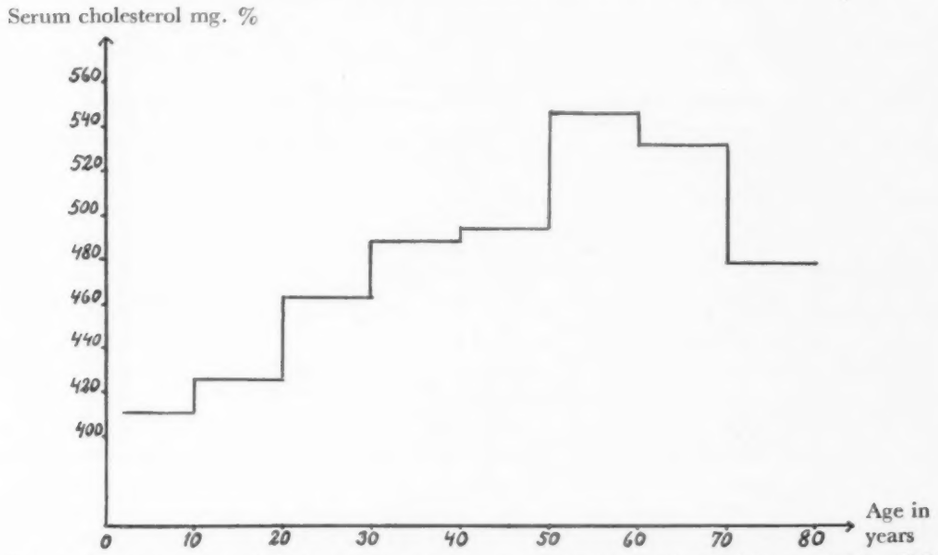


FIG. 1. Average serum cholesterol values by age groups in 110 patients with essential familial hypercholesterolemia.

80 per cent in 1954 or at death. Extrapalpebral xanthomas (tuberosum or tendinosum) were encountered in 50 per cent in 1941 to 1943 and in 68 per cent in 1954 or at death. Xanthelasma palpebrarum was observed in 28 per cent in 1941 to 1943 and in 50 per cent in 1954 or at death. Arcus senilis occurred in 38 per cent in 1941 to 1943 and in 48 per cent in 1954 or at death. Angina pectoris occurred in 22 per cent in 1941 to 1943 and in 40 per cent in 1954 or at death.

Patients with Essential Familial Hypercholesterolemia Examined in 1954. In addition to the thirty-five re-examined subjects, we found seventy-eight additional cases of the disease. This brings the total number of cases in 1954 to 113, including thirty-one children aged two to fourteen years. The distribution of serum cholesterol values in 110 of these patients is indicated in Figure 1. Three patients were excluded because of the presence of other conditions (diabetes mellitus in two, pregnancy in one) which might influence the level of the serum cholesterol. Figure 1 shows the average cholesterol value for each age group, further defined in Table III.

It is apparent from Table III that the serum cholesterol is lowest during childhood, increases steadily with age, reaches a peak in the decade fifty to fifty-nine, and then again declines. The number of patients in age groups sixty to seventy-nine years is too small to make the difference between the average cholesterol values in the fifty to fifty-nine group and in the sixty to seventy-nine groups significant.

Table IV gives the occurrence of latent xanthomatosis, extrapalpebral xanthoma tuberosum and tendinosum, xanthelasma palpebrarum, arcus senilis and angina pectoris in 112 persons with essential familial hypercholesterolemia examined in 1954 (One diabetic (XI,57) is not included in the analysis, as he presents no evidence of essential familial hypercholesterolemia).

TABLE III

Age Group (yr.)	No. of Patients	Average Serum Cholesterol (mg. %)
2– 9	25	411
10–19	13	426
20–29	10	463
30–39	24	488
40–49	13	494
50–59	15	546
60–69	7	532
70–79	3	478

Hypercholesterolemia without xanthomatosis (latent xanthomatosis) was observed in seventy of the 112 persons, i.e., 62 per cent. As is evident from Table IV, this may be the only manifestation of the disorder in the youngest age groups. With advancing age the incidence of xanthomas increases. The youngest person with xanthomatosis was nineteen years of age. From the age of thirty on, more than half of the subjects had xanthomatosis. In the oldest age groups hyper-

TABLE IV

FOLLOW-UP INFORMATION (1954) ON 112 INDIVIDUALS WITH ESSENTIAL FAMILIAL HYPERCHOLESTEROLEMIA GROUPED ACCORDING TO AGE

Ages	1–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	2–79 (Total)
Findings:									
Hypercholesterolemia	25	13	10	25	13	15	7	4	112
Latent xanthomatosis	25	12	7	12	5	7	1	1	70
Tendinous xanthomas	..	1	3	11	7	6	3	3	34
Extrapalpebral cutaneous xanthomas	..	..	..	2	2	1	1	..	6
Palpebral xanthelasmas	..	..	..	6	4	5	4	1	20
Arcus senilis	..	1	3	5	3	6	6	3	27
Angina pectoris	..	..	..	..	2	3	5	..	10

cholesterolemia without xanthomatosis was exceptional.

The incidence of arcus senilis also increases with age. Angina pectoris was present in ten of the 112 patients; these cases were distributed within the age groups forty to sixty-nine, the frequency increasing with age. In these age groups about twenty-five per cent had angina pectoris. No defects of the cardiac valves were found.

Other Diseases. Thyroid disorders: Six females and two males presented small or moderate, soft, diffuse goiters. All of the patients appeared to be euthyroid. Two women had undergone operations for non-toxic goiter; both appeared euthyroid when seen by us.

In one man with widespread xanthomas of the skin and tendons, who is now fifty-two years of age (V,10), moderately severe thyrotoxicosis developed at the age of 40. In the course of this disease the xanthomas decreased perceptibly in size and at the same time the serum cholesterol dropped from 523 to 214 mg. per cent (cf. Kornerup). After thyroidectomy the xanthomas increased again. At follow-up in 1954 the patient appeared to be euthyroid; the serum cholesterol value was 855 mg. per cent. He had never had cardiac symptoms.

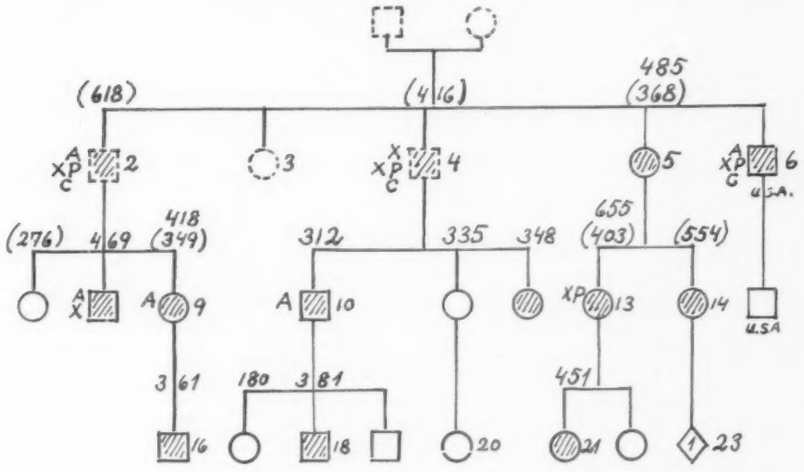
Attacks of cholelithiasis had occurred in ten of the 112 patients, all females. Six had operations for gallstones. As forty-five of the 112 patients are females (over fifteen years of age), the incidence of cholelithiasis among the females is 22 per cent.

Of the seventy-three subjects in whom the blood pressures was measured, eight had systolic as well as diastolic hypertension. This is a maximum figure as the blood pressure was not determined under basal conditions.

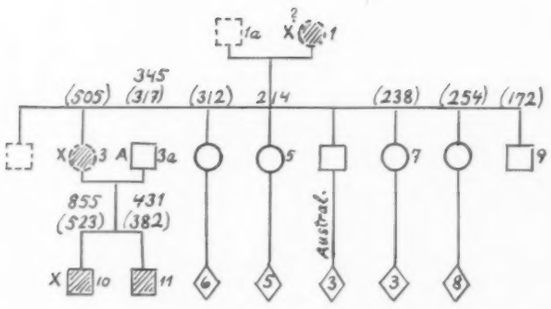
Electrocardiograms (three standard leads and one precordial lead, CF_2) were obtained in seventy-seven cases of hypercholesterolemia. Four exhibited abnormalities: One (I,38) showed the sequelae of a posterior infarct (the patient was having attacks of angina pectoris); one (IX,22, a twenty-seven year old man without cardiac symptoms) had a Wilson block; a seventy-nine year old woman (I,9) with diabetes mellitus had an almost isoelectric T_1 and a slightly delayed conduction time; a forty year old man (VII,21) had rather high P_2 and P_3. This last patient died of coronary thrombosis at the age of forty-one. Autopsy showed, among other things, widespread xanthomatosis of the pulmonary arteries. (This case will be published separately.)

In all 112 cases we looked for *xanthomas of the oral mucosa*. One patient (X,9) had a number of elevated, yellowish elements, as large as millet seeds, on the inside of the cheeks; no significance can be attributed to this finding without biopsy. One of the 112 patients had *diabetes mellitus* (I,9). As already mentioned, another patient with diabetes mellitus (XI,57) was excluded from the material, as the cause of hypercholesterolemia in this case was uncertain. *Raynaud's phenomenon* was observed in one of the subjects (II,16), a fifty-three year old woman with high serum cholesterol and frequent inflammations of the fingers and toes.

Only a rough estimate can be given of the time at which the various xanthomatous skin manifestations appeared. In fifteen cases, living and dead, extrapalpebral xanthomas were ob-



PEDIGREE III.



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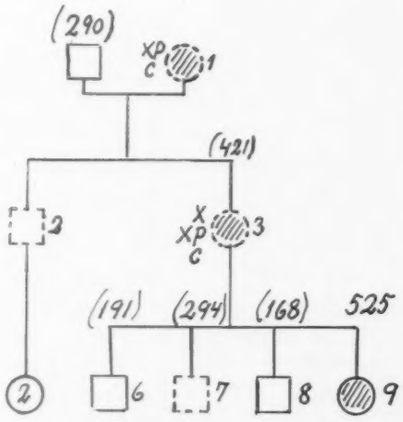


PEDIGREE VI.

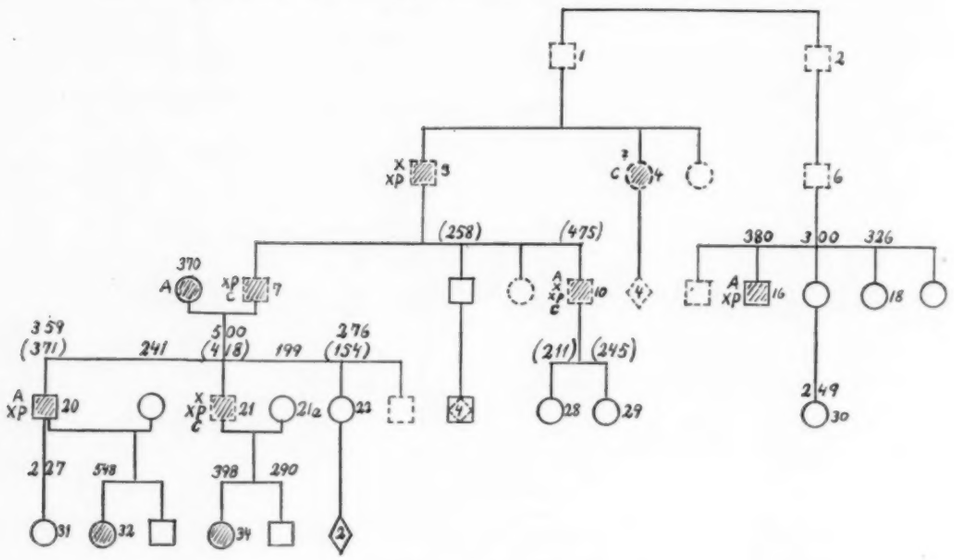
served for the first time by the patient or the physician at the following ages: three, fourteen, twenty-one, twenty-five, twenty-six, twenty-seven, twenty-eight, thirty, thirty, thirty-three, forty, forty-two, fifty, seventy-two and seventy-eight, averaging thirty-five years. In seventeen cases we know the time at which xanthelasma palpebrarum was observed for the first time, i.e., from nineteen to sixty-four years of age, averaging forty-two years.

COMMENTS

Regarding the heredity of essential familial hypercholesterolemia, our study gives solid support to Kornerup's interpretation of the disease (whether or not it is accompanied by xanthomas) as a dominant inherited character. In a significant number of cases xanthomatosis occurred in the offspring of subjects with hypercholesterolemia and their normal spouses. This applies, for example, to the offspring of I_{25}, $VIII_4$, X_2, XI_7 and $XIII_6$ (as well as to the offspring of I_6 and VI_1; one spouse is normal whereas the other has xanthomatosis).

Moreover, the series shows numerous examples of normocholesterolemia among the offspring of persons with xanthomatosis, (e.g., the offspring of XI_7). If a patient with xanthomatosis were to represent the homozygous abnormal, as claimed by Wilkinson et al., all the offspring of this patient would have to be hypercholesterolemic.

The occurrence of homozygosis cannot be considered proved but, as pointed out by Kornerup, the possibility may be considered in II_{38}—a feeble-minded young man in whom, from the age of three, monstrous xanthomas had been developing and in whom death occurred suddenly at the age of eighteen, probably from coronary occlusion. His parents, both of whom had hypercholesterolemia, were first cousins.



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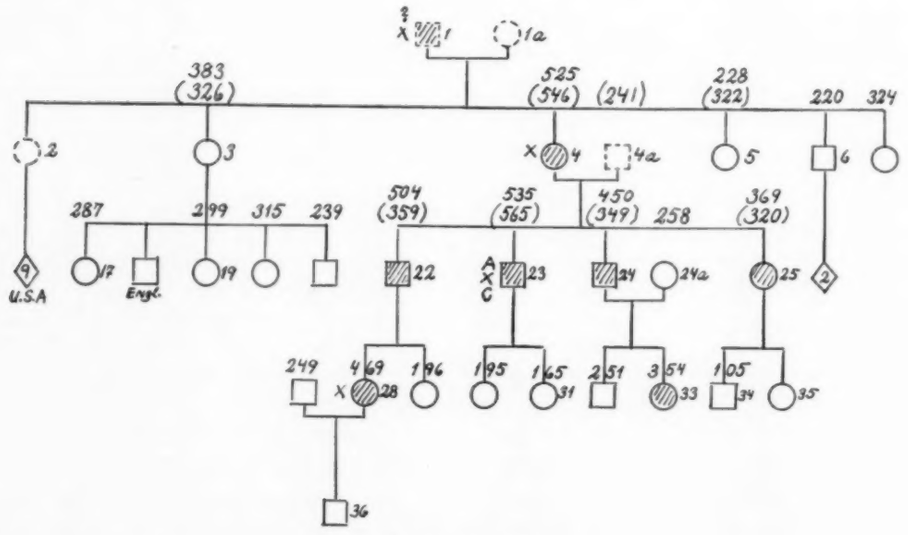
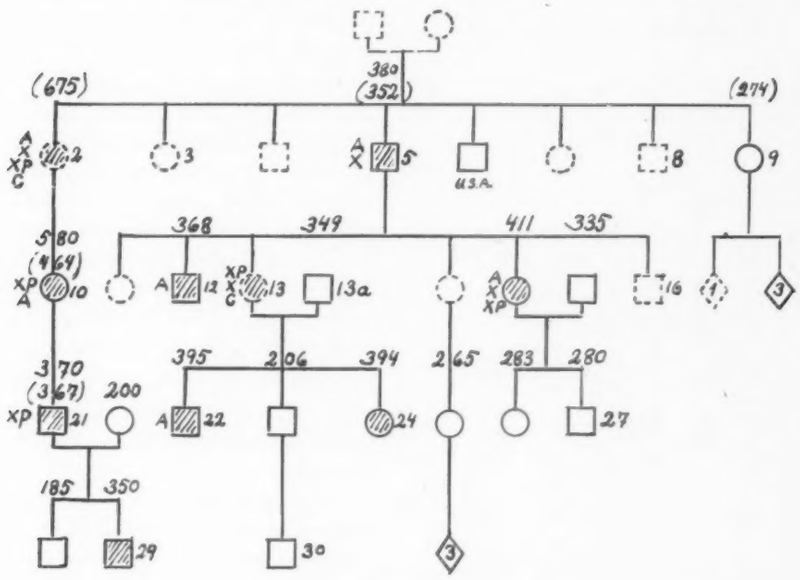


PEDIGREE VIII.

In order to investigate whether extremely widespread xanthomatosis represents homozygosis, let us consider the pattern of heredity in three of the most severe cases of our series. No. 10 in family V had a very high serum cholesterol and widespread, large xanthomas, but no heart disease. His mother had xanthomatosis whereas his father did not, and his serum cholesterol was 317 mg. per cent in 1943 and 345 mg. per cent in 1954. It is rather unlikely that there should be homozygosis in V_{10} but this possibility cannot be ruled out. No. 23 in family VIII had widespread xanthomas, high serum cholesterol and angina pectoris. One of his parents and both his children had normal serum cholesterol. Homozygosity can be ruled out. No. 21 in family VII had high serum cholesterol, moderate xanthomatosis tendinosum and tuberosum, and widespread xanthomatosis of the aorta, coronary arteries and pulmonary arteries. He died at the age of forty-one of coronary occlusion. As one of his children is normocholesterolemic, homozygosity can also be ruled out in his case.

From these observations it may be concluded that even widespread xanthomatosis of the skin, tendons, coronary arteries and aorta is com-



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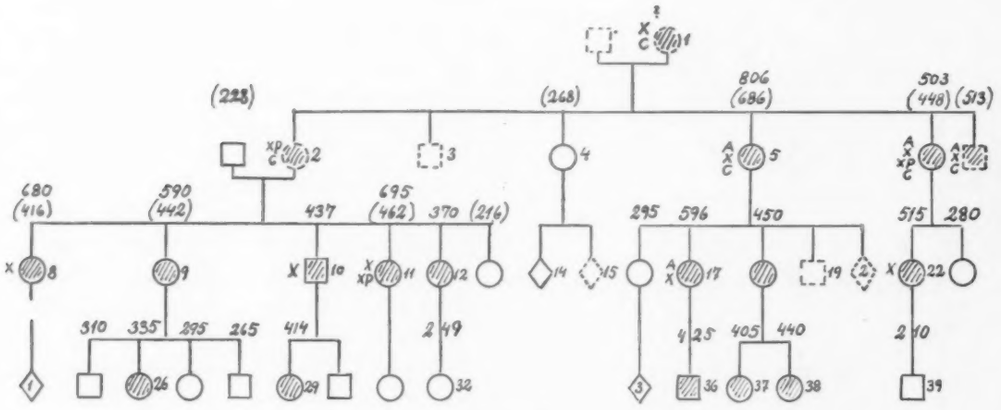
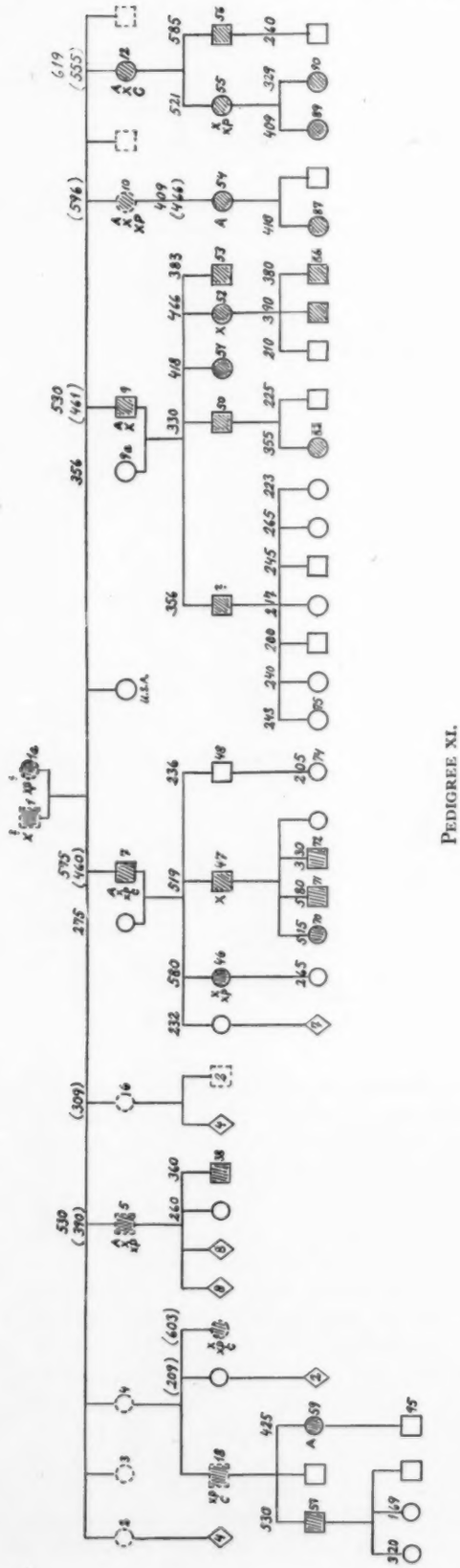


PEDIGREE X.

patible with heterozygous occurrence of the abnormal gene.

Kornerup's assumption that the serum cholesterol increases from childhood on has been confirmed by our examination of sixty-five children (ranging in age from two to fourteen) of marriages in which one of the parents was hypercholesterolemic. While thirty-four of these children presented normal serum cholesterol, high values were observed in thirty-one, i.e., in 48 per cent. This corresponds to the expected incidence in dominant heredity. (The children of XI_{49} were not included in this analysis as it is doubtful that XI_{49} has essential familial hypercholesterolemia).

Figure 1, showing the mean values of serum cholesterol in the various age groups from two to seventy-nine years, indicates a gradual rise up to the age of fifty to fifty-nine and then a fall. Comparing this figure with Keys' representation of the serum cholesterol values in 1,492 normal men, we find that the shape of the curve seems to be the same for both groups, Keys also describing a gradual rise with a summit at fifty-five years of age, with subsequent decline. Thus the factors which are responsible for the fall in serum cholesterol in normal men after the age of fifty-five may also apply to persons with hypercholesterolemia. These factors are unknown. The fall in cholesterol in elderly subjects may be a normal phenomenon of aging but it may also partially be explained by the fact that elderly people with high cholesterol values present signs of coronary disease and are therefore not in-



PEDIGREE XI.

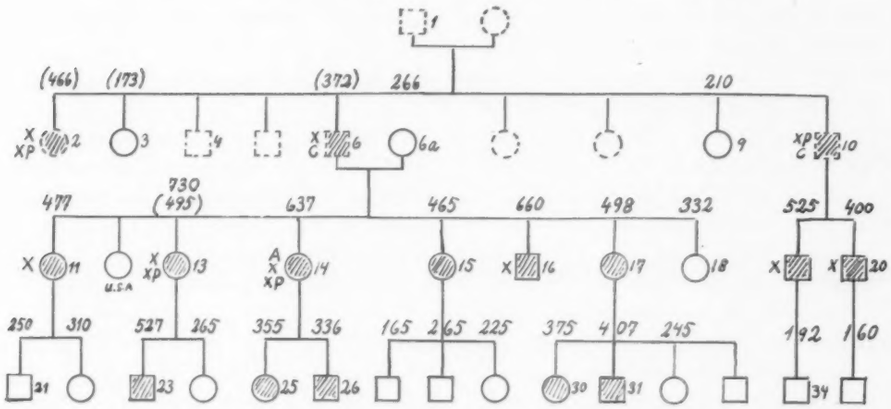
cluded in an analysis of cholesterol values in normal subjects. Our study does not contribute to the solution of this problem.

Keys and also Sperry and Webb followed a number of normal subjects for varying periods of time. Keys found that the serum cholesterol of persons aged forty-six rises within a four-year period whereas in persons aged fifty-four there is a fall within a four-year period. Sperry and Webb re-examined twenty-two subjects thirteen to fifteen years after the first determination of serum cholesterol. They found no essential change in ten but twelve exhibited an increase of 15 to 30 per cent (at the time of follow-up the subjects were from thirty-two to fifty-seven years of age).

As emphasized by previous authors (Müller and others) coronary disease and sudden death (often at an early age) occur more frequently in families with essential familial hypercholesterolemia than in the general population. In the follow-up of fifty hypercholesterolemic patients from Kornerup's series we found that ten (20 per cent) had died from coronary occlusion in the course of twelve years. The average age of the deceased persons was 47.2 years. It must be presumed, however, that 20 per cent is a somewhat higher percentage than is to be expected in such families, as four of the deceased were probands in Kornerup's families, and probands are often more severely affected by the disease than the other members of the family.

Moreover, the follow-up of Kornerup's patients showed that xanthomatosis increases in frequency with advancing age. Our follow-up study, for instance, revealed that 80 per cent of the subjects exhibited this manifestation. As the remaining 20 per cent (ten persons) with latent xanthomatosis (hypercholesterolemia without xanthomas) belong mostly to the youngest age groups and therefore the possibility that xanthomas will develop at some future date exists, it must be assumed that in *at least 80 per cent* of the patients with essential familial hypercholesterolemia xanthomatosis will develop in the course of time.

If xanthomas do not occur until an advanced age they generally do not develop extensively, but hypercholesterolemia without xanthomatosis is the exception among elderly persons, whereas it is the rule in children and younger adults. A moderate elevation in serum cholesterol (400 mg. per cent) in a young person allows no prediction as to whether or not xanthomatosis will develop



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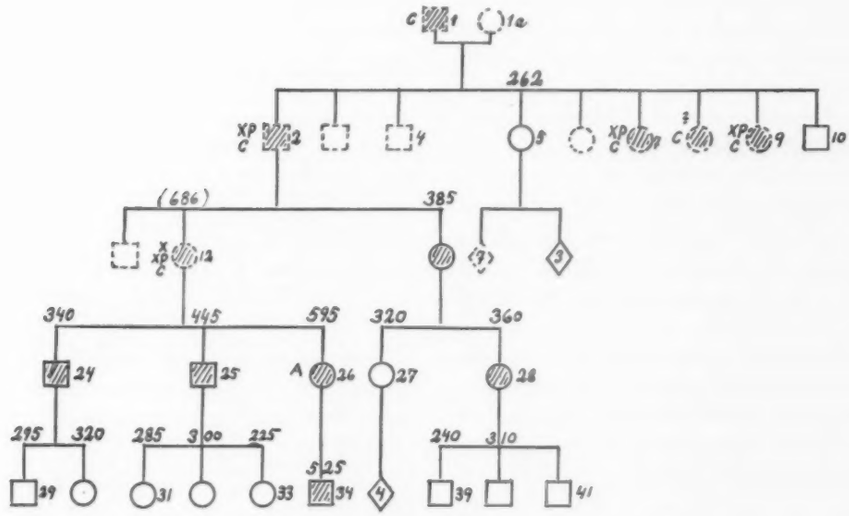

PEDIGREE XIV.

in later life. A very high serum cholesterol, on the other hand, is practically certain to be accompanied by manifest xanthomatosis with advancing years. In the individual patient, xanthomatosis has a tendency to progress; regression is exceptional.

Raynaud's phenomenon was demonstrated in one patient who had often had inflammation of the fingers and toes. Lynn, Steiner and Van Wyk's arteriographic studies of the digital arteries in patients with Raynaud's disease have shown that nutritional disturbances in the digits occurred only in the presence of an organic, occluding lesion. Hence it seems reasonable to presume that the Raynaud phenomenon in our patient was due to xanthomatous deposits in the digital arteries.

SUMMARY

In 1954 the authors conducted a follow-up study of fifty persons with essential familial hypercholesterolemia, representing twelve families, who had previously been studied (1941 to 1943) by Kornerup. A total of seventeen (34 per cent) had died in the intervening period; ten (20 per cent) of coronary occlusion (at an average age of 47.2 years) and seven (14 per cent) of other diseases (at an average age of sixty-six years). The average age of the thirty-three survivors in 1954 was 48.5 years.

Xanthomas of tendons and/or skin, including xanthelasmata palpebrarum, were present in 64 per cent in 1941 to 1943 and in 80 per cent in 1954 or at death. Extrapalpebral xanthomas (tuberosum or tendinosum) occurred in 50 per

cent in 1941 to 1943 and in 68 per cent in 1954 or at death. Xanthelasmata palpebrarum were observed in 28 per cent in 1941 to 1943 and in 50 per cent in 1954 or at death. Arcus senilis was observed in 38 per cent in 1941 to 1943 and in 48 per cent in 1954 or at death. Angina pectoris was present in 22 per cent in 1941 to 1943 and in 40 per cent in 1954 or at death.

Systematic examination of almost all of the members of these twelve families in 1954 revealed that 112 individuals, ranging in age from two to seventy-nine years, had hypercholesterolemia. (Nearly one-third of them are also included in the aforementioned follow-up study). Latent xanthomatosis, i.e., hypercholesterolemia without xanthomas, was observed in seventy (63 per cent), tendinous xanthomas were found in thirty-four (30 per cent), extrapalpebral cutaneous xanthomas in six (5 per cent), palpebral xanthelasmas in twenty (18 per cent), arcus senilis in twenty-seven (24 per cent), and angina pectoris in ten (9 per cent).

Hypercholesterolemia *without* xanthomatosis is the rule in children and young adults; hypercholesterolemia *with* xanthomatosis in older adults. In each individual xanthomatosis has a tendency to progress, regression being exceptional.

Hypercholesterolemia is present from childhood. The serum cholesterol increases steadily from childhood until the fifth decade, after which it seems to decrease. This corresponds with the findings in normocholesterolemic persons (cf. Keys).

Essential familial hypercholesterolemia is transmitted as a dominant. The occurrence of xanthomas is *not* conditioned by homozygous heredity but depends largely upon the level of serum cholesterol.

Angina pectoris is common and coronary occlusion is the most common cause of (sudden) death, often at a relatively early age.

Acknowledgments: We wish to express our thanks to the heads of various hospital departments for having placed case records at our disposal and to Søren Aggebo, M.A. (econ.) of the Aarhus University for the statistical calculations and the preparation of the graph.

REFERENCES

1. Adlersberg, D., Parets, A. D. and Boas, E. P. Genetics of atherosclerosis. Studies of families with xanthoma and unselected patients with coronary artery disease under the age of fifty years. *J. A. M. A.*, 141: 246, 1949.
2. Brun, G. C. Cholesterol content of the red blood cells in man (diss.). *Acta med. Scandinav.*, suppl. 99, pp. 3–237, 1939.
3. Keys, A. The age trend of serum concentrations of cholesterol and of Sf. 10–20 ("G") substances in adults. *J. Gerontol.*, 7: 201, 1952.
4. Keys, A., Mickelsen, O., Miller, E. v. O., Hayes, E. R. and Todd, R. L The concentration of cholesterol in the blood serum of normal man and its relation to age. *J. Clin. Investigation*, 29: 1347, 1950.
5. Kornerup, V. Familiaer Hypercholesterolaemi og Xanthomatose (Diss.). Kolding, Denmark, 1948.
6. Müller, C. Xanthomata, hypercholesterolemia, angina pectoris. *Acta med. Scandinav.*, Suppl. 139, p. 75, 1938.
7. Müller, C. Angina pectoris in hereditary xanthomatosis. *Arch. Int. Med.*, 64: 675, 1939.
8. Lynn, R. B., Steiner, R. E. and Van Wyk, F A. K. Arteriographic appearances of the digital arteries of the hands in Raynaud's disease. *Lancet*, 1: 471, 1955.
9. Sperry, W. M. and Webb, M. The effect of increasing age on serum cholesterol concentration. *J. Biol. Chem.*, 187: 107, 1950.
10. Wilkinson, C. F., Jr., Hand, E. A. and Fliegelman, M. T. Essential familial hypercholesterolemia. *Ann. Int. Med.*, 29: 671, 1948.

Rheumatic Tricuspid Stenosis*

A Clinical and Physiologic Study with a Suggested Method of Diagnosis

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ALTHOUGH rheumatic involvement of the tricuspid valve clinically is considered an uncommon lesion, studies of postmortem material suggest a more frequent incidence.[1–5] These and additional investigations indicate that structural distortion of the tricuspid valve and its supporting elements generally occurs in association with other valvular lesions,[2,4,6,7] and produces concomitant regurgitation and stenosis, either of which may be dynamically significant. Failure to recognize tricuspid disease stems in part from the fact that the right heart and systemic venous bed bear the burden of remarkable alterations in hemodynamics without manifestations distinctive from those due to coexisting valve defects. With current refinements in technics and the availability of methods for surgical correction to tricuspid valve deformities,[8] recognition of tricuspid lesions has become a matter of practical importance.

To date few studies have been made on the altered circulatory dynamics in patients with rheumatic tricuspid stenosis.[9–11] The purpose of this paper is to report the physiologic and clinical pattern derived from an analysis of thirteen patients with proved rheumatic tricuspid stenosis. In the interest of advancing precise diagnostic technics, a new method is also described whereby the size of the tricuspid orifice may be estimated during right heart catheterization.

MATERIAL

The thirteen patients investigated had chronic rheumatic heart disease and were being evaluated for cardiac surgery. The anatomic presence of tricuspid disease was established, with one exception, by direct exploration of the valve at operation in ten cases and at necropsy in two. In either method of examination anatomic stenosis was diagnosed when the orifice did not permit the passage of at least one and a half fingers, an area calculated as less than 3.5 cm.^{2}. Only one orifice was considered as large as this minimal requirement. In the single patient in whom exploration was not feasible, stenosis was diagnosed by the presence of a diastolic thrill palpable over the exposed surface of the right ventricle during surgery.

Tricuspid regurgitation was determined only at the time of surgery and was acknowledged when a jet was felt by the surgeon (C. P. Bailey) during ventricular systole. The regurgitation was grade 1 to 4 +, and was considered significant when it was greater than 2 +. Significant regurgitation was found in only one case (F. B.).

The anatomic diagnoses are listed in Table II. All but one of the group had additional valve defects which required previous surgery or multiple commissurotomies at the time of the study.

METHODS

The history, physical examination, findings at fluoroscopy, x-rays of the heart and the electrocardiogram were recorded in all cases. Ten patients were studied by catheterization of the right side of the heart. The pressures were measured with electromanometers (Sanborn), and recorded on a direct polyoscillograph (Sanborn). The zero level was taken as 5 cm. below the angle of Louis. Blood samples were analyzed for oxygen content according to the method of Van Slyke and Neill[12] and the oxygen content of the air expired was determined on the Pauling analyzer. Cardiac output was calculated by the direct Fick method. Other estimations included pulmonary arteriolar resistance, effective work of the right ventricle, and tricuspid valve area according to Gorlin and Gorlin.[13]

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RESULTS

Clinical Findings. The clinical data are summarized in Table I. Twelve of the thirteen patients were women. Eleven gave a specific history of past rheumatic activity.

TABLE I
CLINICAL FINDINGS IN THIRTEEN CASES OF TRICUSPID STENOSIS

History of rheumatic fever	11
Exertional dyspnea	11
Peripheral edema	11
Orthopnea	7
Hemoptysis	4
Embolic phenomena	4
Angina	3
Cervical vein distention	8
with systolic pulsations	3
Hepatomegaly	8
with systolic pulsations	2
Ascites	4
Jaundice	2
Cyanosis	2
Pulmonary rales	2

The subjective manifestations were slowly progressive in all patients and had been present for an average of 9.8 years prior to this study. Exertional dyspnea, resulting in serious incapacitation, was present in eleven patients, and in each instance was the initial discomfort experienced. In contrast, paroxysmal nocturnal dyspnea was present in a single case only. Peripheral edema occurred with the same frequency as dyspnea but ascites was noted by only four patients. The third most common symptom, easy fatiguability, appeared in ten patients. Hemoptysis, embolic phenomena, and the pain of coronary artery insufficiency were unusual events; the latter was noted only when aortic stenosis was a concomitant lesion. Syncope did not occur in a single individual, nor was acute pulmonary edema reported by any patient in this series.

The blood pressure levels were within normal limits in the entire group. Marked distention of the cervical veins was observed in eight patients; in three, systolic pulsations were seen. At the time of the initial examination the liver was enlarged in eight cases; systolic pulsations were discernible in two. While the findings of pulmonary congestion were observed on only two occasions, the classic picture of anasarca and clear lung fields was noted in only one patient. Obvious cyanosis and minimal jaundice were present, each in two cases, but a combination of both was not seen.

The auscultatory events essentially were those of the associated valvular lesions. Although a mid-late diastolic murmur was reported at the tricuspid area in five patients, it could not be identified as originating at that area because in all of these cases mitral stenosis was a significant lesion.

Normal sinus rhythm was present in seven patients, atrial fibrillation in the other members of the group. Of the patients with normal sinus rhythm, six had abnormal P waves in the electrocardiogram. Three tracings were indicative of right ventricular hypertrophy and strain. The only patient with aortic, mitral and tricuspid stenosis had an electrocardiogram compatible with combined left and right heart strain.

Moderate to marked cardiac enlargement was revealed in the roentgen studies of all patients. The films were carefully reviewed in an effort to demonstrate enlargement of the right atrium. This was possible in two cases from an enlargement of the lower right cardiac border in the postero-anterior view and/or elongation of the right auricular appendage in the left anterior oblique view. In two cases increase in size of the right atrium was clearly indicated in the right anterior oblique view. This appeared to be the most reliable sign of right atrial enlargement even though it is infrequently seen. Angiocardiography performed in one patient revealed enlargement and delay in emptying of the right atrium.

Physiologic Findings. The physiologic data obtained in ten cases are summarized in Table II. The oxygen consumption taken while the patients were at rest ranged between 127 and 257 cc./minute. The arteriovenous oxygen difference ranged between 4.9 and 11.2 volumes per cent, with abnormal elevations in six cases. The cardiac index while the patient was at rest was below the normal of 2.6 L./m/M^2 in seven cases. The effect of exercise upon the cardiac output was studied in two patients; in both the cardiac index failed to increase during the exercise state.

The mean pulmonary artery pressures were within normal limits in two cases, moderately elevated in six, and markedly elevated in one. The effect of exercise upon the pulmonary artery pressure was observed in three patients, in one of whom the values were within normal limits while the patient was at rest. The pressure rose to hypertensive levels in all three. The pulmonary capillary wedge pressure was elevated in five of

TABLE II

PHYSIOLOGIC DATA

Patients	Final Diagnosis†	O_2 Consumption (cc./min.)	A-V O_2 Difference (vol. %)	Cardiac Output (L/min.)	Cardiac Index (L/min./M^2)	Brachial Arterial O_2 Saturation	Pressures (mm. Hg)					Effective Right Ventricular Work (kg.m./min.)	Tricuspid Valve Area, $Cm.^2$	
							Pulmonary Venous Capillary	Pulmonary Artery	Right Ventricle	Right Atrium	Pulmonary Arteriolar Resistance (dynes sec $cm.^{-5}$)		Calculated[13]	Estimated
F. B.*	M.S., A.S., M.I., T.S., T.I.	175	7.8	2.2	1.4	88	19	57/20 (37)	58/9	R E (10) (27)	655	0.74	0.58	1.80
M. T.	M.S., A.S., T.S.	163	6.5	2.5	1.7	85	27	42/25 (34)	40/0	(6)	224	0.83	1.27	0.95
A. H.	M.S., T.S.	...	....	...	....	..	..	.....	....	(16)	...	....	....	....
M. P.	M.S., A.S., T.S., T.I.	154	11.2	1.4	1.0	92	..	120/70 (90)	120/15	(20)	...	1.29	0.48	1.80
R. R.	M.S., T.S.	257	11.4	2.3	....	90	10	20/10 (15)	28/0	(3)	174	....	0.62	0.20
B. S.	M.S., A.S., T.S., ? T.I.	147	7.0	2.1	1.23	94	18	36/15 (25)	33/5	(8)	267	0.94	0.84	N. E.§
S. L.	A.S., M.S., T.S.	157	4.9	3.2	1.9	88	9	R E 29/11 (20) 40/20 (25)	30/1	(4)	276	0.54	1.07	3.5
H. N.*	M.S., T.S.	R‡ E 260 440	R E 5.5 9.6	R E 4.7 4.6	R E 3.2 3.1	92	..	R E 45/15 (25) 55/38 (44)	R E 47/0–10 60/8–10	R E (12) (26)	...	R E 1.15 1.95	1.02	2.3
L. P.	M.S., T.S.	127	6.0	2.1	1.4	94	18	32–45/15–20 (25)	32–45/8	(22)	266	0.50	0.31	2.0
B. W.*	M.S., T.S.	R E 147 344	R E 6.5 11.6	R E 2.3 3.0	R E 1.5 1.9	92	R E 12 20	R E 20/11 (18) 38/19 (27)	18/−5	(10)	208	R E 0.39 0.74	0.27	0.95

* In these patients exercise data were obtained; in all others the data above refer to the resting state.

† M.S. = mitral stenosis; A.S. = aortic stenosis; M.I. = mitral regurgitation; T.S. = tricuspid stenosis; T.I. = tricuspid insufficiency.

‡ R = rest; E = exercise.

§ N.E. = not estimated.

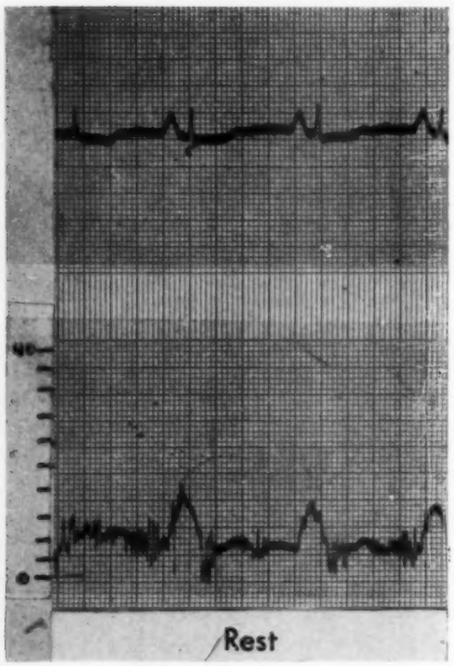

FIG. 1. Patient B. W. Right atrial pressure curve (below) showing giant "a" waves during rest. Lead II of electrocardiogram is above.

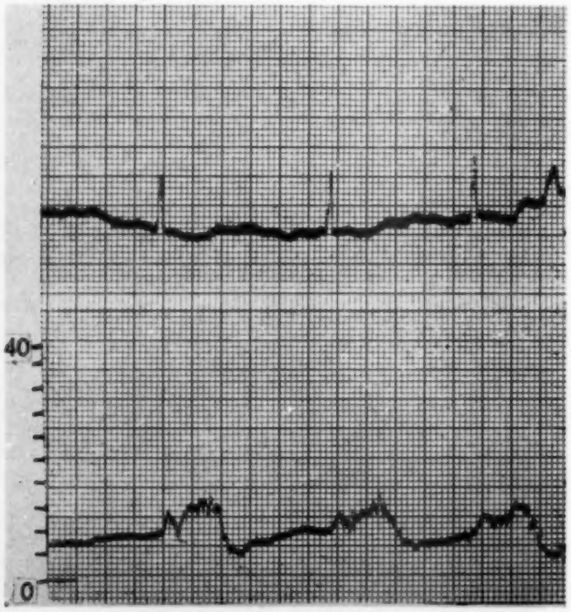

FIG. 2. Right atrial pressure curve (below) showing "ventricularization" in patient F. B. who had tricuspid stenosis and regurgitation.

the seven patients in whom the determination was made at rest. The pulmonary arteriolar resistance was elevated in five patients. Evidence of failure of the right side of the heart was suggested by an elevated end-diastolic pressure in the right ventricle in four patients, one of whom (F. B.) had associated tricuspid regurgitation.

The mean right atrial pressure was markedly elevated in eight patients at rest. This abnormality was exaggerated by exercise in the two in whom this measurement was obtained during the exercise state.

Two types of right atrial pressure curves were observed. The first consisted primarily of three elements: an exaggerated positive wave (a wave) produced during atrial systole was usually followed by a negative deflection (x wave) occurring during early ventricular systole and then by a gradually ascending positive wave in the latter phase of ventricular systole (v wave). In essence, therefore, this pressure curve simulated that produced by the normal atrium except for the exaggerated "a" wave. (Fig. 1.) This was found in all patients with normal sinus rhythm, none of whom had significant tricuspid regurgitation.

The second type was characterized by an absent "a" wave, a small positive wave (c), with an attenuated or absent negative wave during early ventricular systole followed by a sharply rising positive wave (v) in the latter part of this phase of the cardiac cycle. This, therefore, resembled the curve produced by the normal functioning ventricle. It was observed in three patients, each with atrial fibrillation, one of whom had marked tricuspid regurgitation. (Fig. 2.)

A pressure gradient across the tricuspid orifice was demonstrated in seven of the nine patients in whom both right atrial and right ventricular pressures were recorded. (Fig. 3, Table III.) In general, the gradient was greater during early and mid-diastole. The smallest gradient was observed in the patient with significant regurgitation (F. B.). In the two patients in whom a gradient could not be obtained, the electrocardiogram was not recorded at the time the pressures were determined, because of technical difficulties, and the tracings could not be superimposed upon one another. However, on examination of our records it was apparent that the right atrial pressure was consistently higher than that of the right ventricle during diastole. In one patient (H. N.) employment of a double-lumen catheter made it possible to record pressure gradients during exercise as well as at rest. The atrioventricular gradient was greatly increased by exercise. (Fig. 4.)

That tricuspid commissurotomy may mark-

TABLE III

ATRIOVENTRICULAR PRESSURE GRADIENTS DURING VENTRICULAR DIASTOLE IN PATIENTS WITH TRICUSPID STENOSIS (MM. HG)

Patient	Early Diastole			Mid Diastole			Late Diastole		
	Right Atrium	Right Ventricle	A-V Gradient	Right Atrium	Right Ventricle	A-V Gradient	Right Atrium	Right Ventricle	A-V Gradient
F. B.	4	0	4	5	2	3	7	7	0
M. T.	5	2	3	14	4	10	5	2	3
M. P.	18	10	8	24	10	14	20	14	6
R. R.	10	0	10	12	0	12	15	−2	17
B. S.	5	2	3	10	2	8	7	5	2
H. N.	R 14	2	12	12	4	8	13	8	5
	E 20	1	19	20	7	13	20	9	11
B. W.	15	−5	20	14	−10	24	20	−8	28

edly reduce the atrioventricular pressure gradient and eliminate the exaggerated "a" wave is shown in Figure 5.

When the tricuspid valve area was calculated by the Gorlin formula the determination did not correlate well with the size of the orifice estimated at the time of surgery. (Table I.)

DISCUSSION

It is abundantly clear that the association with other and significant valve involvement qualifies the validity of the present study of the physiologic and clinical characteristics of rheumatic tricuspid disease. However, since these are the circumstances under which tricuspid lesions are most likely to occur, they represent the conditions under which an inquiry into the diagnostic features of the disease must be made.

Of the three methods used to define significant stenosis two, surgical and postmortem exploration of the valve, are entirely acceptable. A diastolic thrill over the right ventricle may be related to the intensity and duration of the murmur rather than to the magnitude of the lesion. The decision to accept the thrill as an indication of significant involvement was based on its presence in all instances in which the right ventricle was exposed and the valve was found to be stenotic, and by the realization that a diastolic thrill over the apex of the left ventricle is a constant finding in dynamic mitral stenosis. In one patient not in this series, in whom this criterion was applied, pulmonary regurgitation, the only other valvular lesion capable of producing an identical thrill, was present.[14]

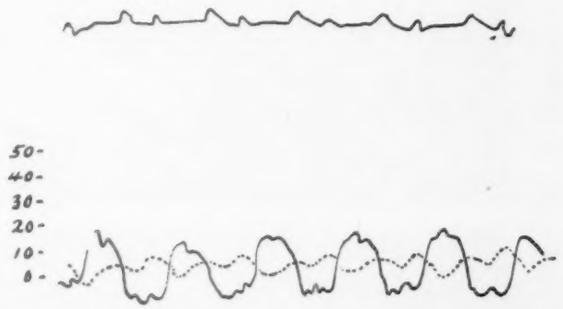

FIG. 3. Right atrial and right ventricular pressure curves (lower) superimposed to show atrioventricular gradient during diastole. Broken line is the right atrial pressure.

The direct method of estimating the quantity of regurgitation and, therefore, its significance, is not entirely reliable because it depends on variable factors such as the force of ventricular contraction when the patient is under anesthesia and the heart is undergoing manipulation, the integrity of the circulation at the time of examination, and the accuracy of the surgeon's exploring finger. There is no exact information as to what quantity of regurgitation represents a significant lesion. In spite of these objections, this method remains the only direct means of examination, and, as such, is useful.

In the search for definitive indications of significant obstruction at the tricuspid orifice, the present investigation emphasizes the importance of alterations in the normal right atrial pressure curve and the demonstration of a pressure gradient across the valve during ventricular diastole. These findings are in agreement with those of Ferrer et al.[9] and McCord et al.[11]

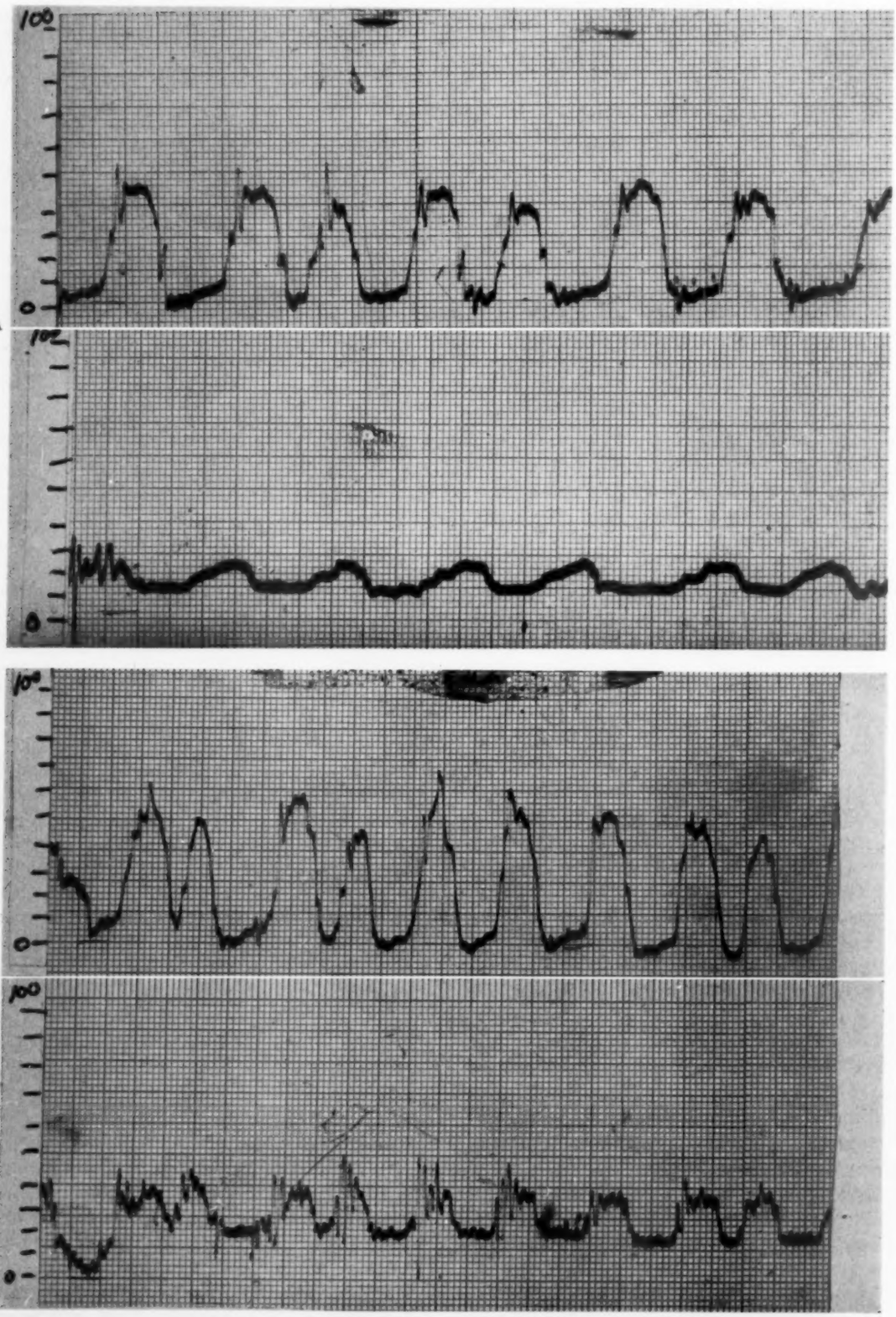

FIG. 4. Patient H. N. A, right ventricular (upper) and right atrial pressure curves at rest; these recordings were not made simultaneously. B, right ventricular and right atrial pressure curves recorded simultaneously through a double lumen catheter immediately after exercise. Note increase in atrioventricular gradient.

Unequivocal evidence is offered that an exaggerated "a" wave is produced when the tricuspid orifice is stenosed in patients with normal sinus rhythm. This distinctive finding undoubtedly results from the forceful contraction of the muscle fibers which have become lengthened in response to the increased volume of blood contained within the incompletely emptied atrium. However, this type of pressure wave obviously is not produced in the presence of atrial fibrillation and, for that reason, if relied upon as the sole indication of tricuspid stenosis would have been misleading in almost half the patients in this series. Furthermore, an exaggerated atrial systolic pressure wave has been observed in patients with right ventricular hypertension secondary to pulmonic stenosis and atrial septal defect.[15,16] Finally, it has been our experience that a similar finding appears in patients with isolated mitral stenosis who have associated pulmonary and right ventricular hypertension and normal sinus rhythm. Hence the exaggerated "a" wave, although characteristically observed in patients with tricuspid stenosis with normal sinus rhythm, is not pathognomonic of this lesion.

More significant in the diagnosis of tricuspid stenosis is the presence of an atrioventricular pressure gradient during ventricular diastole. With incomplete opening of the stenosed valve, rapid inflow into the right ventricle does not occur, and filling is accomplished more gradually. This is suggested by the pressure gradient that is constantly observed during this phase of the cardiac cycle. (Table III.) This gradient is not influenced by the cardiac rhythm or unrelated defects. It was not observed in patients with right ventricular hypertension secondary to mitral stenosis without tricuspid disease.

During the exercise state, when there is an increase in the venous return to the heart, the gradient across the tricuspid valve is increased. This is well demonstrated by use of a double-lumen catheter. (Fig. 4.) Another factor to be considered during the exercise state is the concomitant increase in cardiac rate. This results in a reduction of the diastolic filling time. Although in the normal person this may be of little consequence, in patients with tricuspid stenosis it may result in further incomplete emptying of the right atrium. The gradient is thus augmented. This is suggested in one patient (A. H.) whose right atrial pressure rose from 16 mm./Hg when normal sinus rhythm prevailed to 42 mm./Hg during an episode of paroxysmal atrial tachycardia.

The presence of a sustained rise in the right atrial pressure during ventricular systole, so-called "ventricularization," is generally accepted as indicating tricuspid regurgitation.[17,18] The presence of a negative (x) wave during systole excludes regurgitation. A correlation of the contour of the right atrial pressure curve with the presence or absence of regurgitation could be made in three patients. In two (R. R. and A. H.) normal x waves were present. Neither had regurgitation. One patient (F. B.), in whom significant regurgitation was demonstrated at surgery, had "ventricularization" of the right atrial pressure curve. (Fig. 2.)

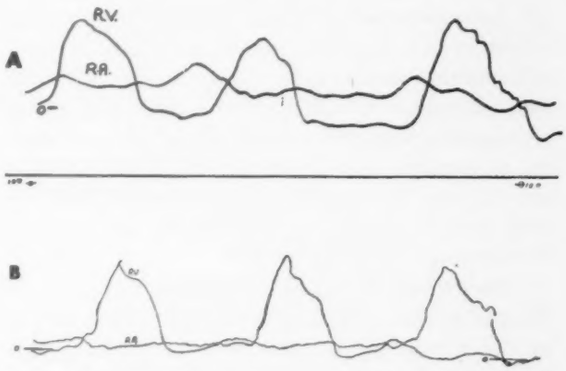

FIG. 5. Patient B. W. A, preoperatively, superimposed right atrial and right ventricular curves. B, three months after tricuspid commissurotomy. Note disappearance of giant "a" waves and marked reduction in the atrioventricular gradient during diastole.

A lack of correlation was noted in four patients. In two (S. L. and B. W.) a minor degree of regurgitation was accompanied by normal x waves in the right atrial pressure curve. In two patients (L. P. and H. N.), both exhibiting atrial fibrillation, there was sustained elevation in the right atrial pressure during ventricular systole, without regurgitation. For an explanation of this apparent lack of correlation, consideration of the following factors is necessary. (1) *Distensibility of the right atrial-caval system:* If the right atrium and vena cava are easily distensible, regurgitation of a considerable jet of blood may cause little or no rise in the atrial pressure. Conversely, a smaller jet may produce a considerable rise in pressure in a rigid atrium. (2) *Pressure-volume relationship of the right atrial-caval system:* If the atrium is filled to near capacity at the time of ventricular systole,

a small amount of regurgitation may result in a marked pressure rise within the atrium. On the other hand, a large regurgitant jet may produce little or no change in pressure when introduced into a depleted atrium. (3) *Quantity of regurgitation:* Theoretically, therefore, ventricularization of the right atrial pressure curve is dependent upon the presence of regurgitation, the quantity of regurgitation flow and the concomitant pressure-volume-distensibility relationship of the right atrial-caval system. In short, this type of atrial curve suggests regurgitation without serving as a quantitative guide and its absence does not negate the presence of regurgitation. A false positive result is more likely when atrial fibrillation is present.

The circulatory dynamics with reference to the pulmonary circulation and cardiac output in this group of patients is determined by the presence of coexisting valvular disease. Pulmonary hypertension, low cardiac output and increased pulmonary vascular resistance are observed in patients with mitral[19] and aortic[20] lesions.

The failure to correlate the valve area as estimated by the Gorlin formula with that estimated by the surgeon probably is due to the fallibility of both methods. The surgeon can detect a deformed, narrowed valve orifice but estimation of the exact area by the exploring finger is difficult indeed. The use of a C-factor of 1 may be too high for calculating the tricuspid orifice. The Gorlin formula breaks down in the presence of regurgitation since the regurgitant flow, and hence the total flow, across the valve is not determinable. Finally, in the present study the flow and pressure gradient across the tricuspid valve were not determined simultaneously and this may have contributed to errors in calculation.

The difficulty in the clinical diagnosis of tricuspid valvular disease stimulated investigation of other diagnostic procedures. A double-lumen catheter with a rubber balloon around the proximal end was employed. The catheter was withdrawn under fluoroscopic control while the balloon, distended with radiopaque dye, was traversing the tricuspid orifice. If the balloon could not negotiate the passage, dye was slowly removed until this was possible. The remainder of the dye was then withdrawn and the amount recorded. The maximum quantity which still permitted the balloon to pass through the tricuspid valve was than re-injected after the catheterization was completed and the size of the balloon measured. This procedure was accomplished in one patient in whom the orifice was estimated preoperatively as 1.8 cm.^{2}, and an identical value was obtained at the time of surgery.

According to the traditional view, pulmonary hypertension and its clinical manifestations are considered to be unlikely developments in patients with tricuspid stenosis. Although this is based upon a sound physiologic concept, its application is restricted to the very rare occasions when tricuspid stenosis is the only cardiac defect present. Significant mitral valve abnormality, which is almost always present, of itself produces serious alterations in pulmonary hemodynamics. It is a reasonable contention, from this study, that tricuspid stenosis does not protect the patient from these changes and certain of their manifestations, most notably exertional dyspnea. However, the failure to encounter acute pulmonary edema in any patient suggests that tricuspid stenosis does attenuate the effects of mitral disease upon the pulmonary circulation. This possibility is not confirmed by an analysis of the pulmonary artery and venous capillary pressures, which reveal the type and magnitude of abnormality found in isolated mitral lesions. Accordingly, it is not justifiable to maintain that tricuspid stenosis seldom is accompanied by the clinical expressions of pulmonary capillary hypertension. It is more accurate to recognize the likelihood of dyspnea and orthopnea, and to relate these symptoms to the presence of associated mitral valvular disease which casts an abnormal physiologic burden on the pulmonary circulation.

The combined presence of peripheral edema, ascites and hepatomegaly has been cited as important evidence of tricuspid stenosis, and attributed mainly to the mechanical dysfunction of the valve and resultant obstruction to the systemic venous blood flow. This concept implies a relation between the degree of stenosis and the manifestations of venous obstruction, and likens the ultimate physiologic effect of tricuspid stenosis to that of constrictive pericarditis. However, in this study the combination of peripheral edema, ascites and hepatomegaly was noted only in four patients and the average size of the valve orifice in these individuals did not differ appreciably from the values obtained in patients who did not present the same clinical findings. An analysis of the catheteriza-

tion data reveals that although the cardiac index is equally impaired in each group, the right ventricular end-diastolic pressures at rest are consistently higher with one exception, in patients with edema, hepatomegaly, ascites, than in those with peripheral edema alone, or with no evidence of fluid retention. Although these facts do not permit a final conclusion, they do suggest that the combination of hepatic enlargement and edema formation occurs in patients with tricuspid stenosis when coexisting mitral involvement or tricuspid insufficiency has precipitated right ventricular failure and, in the absence of that issue, does not appear even though the degree of anatomic tricuspid obstruction is very appreciable.

The present study does not support the contention that a peculiar olive discoloration, attributed to the combined presence of cyanosis and jaundice, is a common or exclusive characteristic of patients with tricuspid stenosis. In the isolated instances in which cyanosis appeared it was the result of a marked increase in arteriovenous oxygen difference and not of a decrease in peripheral arterial oxygen saturation. The causative mechanism, therefore, is related to increased tissue extraction of oxygen and this is common to all types of rheumatic heart disease, including tricuspid stenosis, in which the cardiac output is reduced significantly.

Although jaundice did not appear in any of the group studied, when it does occur it is probably a result of intense hepatic congestion arising from heart failure. Since both cyanosis and jaundice may be produced by advanced rheumatic heart disease, there is little reason to emphasize their simultaneous occurrence as a feature of tricuspid stenosis. A more logical concept relates this finding to the marked reduction in cardiac output and development of right ventricular failure which may take place in any valvular deformity.

The elevation of the central and peripheral venous pressure observed in patients with tricuspid disease is related to obstruction at the tricuspid orifice. An increased atrioventricular pressure gradient is necessary to maintain flow. Hence right ventricular failure need not be held to account for the elevated venous pressure.

Systolic pulsations of the cervical veins and the liver have been emphasized as a feature of tricuspid regurgitation. Since the factors responsible for these pulsations rest with the pressure-volume-distensibility relationships within the atrial cavity and are identical with the genesis of the ventricularization of atrial pressure wave, a singular correlation with the quantity of regurgitation is unlikely.

The total experience in this study indicates that tricuspid stenosis may be clinically obscure and yet produce specific alterations in physiologic data which are useful in recognition of the lesion. Under the circumstances, the stimulus for a definitive diagnostic inquiry must arise from a realization of this fact or from the mere suspicion of tricuspid disease in patients suffering from other forms of rheumatic valve disease, most notably mitral stenosis.

SUMMARY

1. Clinical and physiologic data are presented in thirteen cases of proved rheumatic tricuspid stenosis.

2. The physiologic data of significance included (a) exaggerated "a" waves in the right atrial pressure curves in patients with a normal sinus rhythm and, more important from a diagnostic point of view, (b) significant atrioventricular pressure gradient during ventricular diastole.

3. The significance of the clinical symptoms and signs is discussed.

4. A method for determining the size of the tricuspid orifice during the course of cardiac catheterization is suggested.

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REFERENCES

1. Cooke, W. T. and White, P. D. Tricuspid stenosis with particular reference to diagnosis and prognosis. *Brit. Heart J.*, 3: 147, 1941.
2. Smith, J. A. and Levine, S. A. The clinical features of tricuspid stenosis. *Am. Heart J.*, 23: 739, 1942.
3. Garvin, C. F. Tricuspid stenosis: incidence and diagnosis. *Arch. Int. Med.*, 72: 104, 1943.
4. Aceves, S. and Carral, R. The diagnosis of tricuspid valve disease. *Am. Heart J.*, 34: 114, 1947.
5. Zeisler, E. B. Tricuspid stenosis, review of the literature and report of a case with antemortem diagnosis. *Am. Heart J.*, 8: 697, 1933.
6. Osler, W. and Gibson, A. G. Diseases of the valves of the heart. In: Modern Medicine, by Osler and McCrae. Philadelphia, 1915. Lea and Febiger.
7. Einsel, I. H., Feil, H. S. and Stone, C. S. Clinical and pathological study of 70 cases of mitral stenosis. *Ohio State M. J.*, 27: 783, 1931.
8. Trace, H. D., Bailey, C. P. and Wendkos, M. H.

Tricuspid valve commissurotomy with a one year follow-up. *Am. Heart J.*, 47: 613, 1954.

9. Ferrer, M. I., Harvey, R. M., Kuschner, M., Richards, D. W. and Cournand, A. Hemodynamic studies in tricuspid stenosis of rheumatic origin. *Circulation Res.*, 1: 49, 1953.
10. Tourniaire, A., Blum, J. B., Deyrieux, F. and Tartuilier, M. Diagnostic de la stenose tricuspidienne par catheterisme cardiaque. *Arch. mal. cœur.*, 46: 1008, 1953.
11. McCord, M. C., Swan, H., Blount, S. G. Tricuspid stenosis: clinical and physiologic evaluation. *Am. Heart J.*, 48: 405, 1954.
12. Van Slyke, D. D. and Neill, J. M. Determination of gases in blood and other solutions by vacuum extraction and manometric measurement. *J. Biol. Chem.*, 61: 523, 1924.
13. Gorlin, R. and Gorlin, S. G. Hydraulic formula for calculation of the area of the stenotic mitral valve, other cardiac valves and central circulating shunts. *Am. Heart J.*, 41: 1, 1951.
14. Dickens, J. and Goldberg, H. Pulmonary regurgitation. Case report. To be published.
15. McCord, M. C., Komesu, S. and Blount, S. G., Jr. The characteristics of the right atrial pressure was associated with right ventricular hypertrophy. *Am. Heart J.*, 45: 706, 1953.
16. Goldberg, H. and Downing, D. F. The physiological and clinical changes following closure of atrial septal defects by atrio-septo-pexy. *Am. Heart J.*, 49: 862, 1955.
17. McCord, M. C. and Blount, S. G. The hemodynamic pattern in tricuspid disease. *Am. Heart J.*, 44: 671, 1952.
18. Sepulveda, G. and Lukas, D. S. The diagnosis of tricuspid insufficiency. Clinical features in 60 cases with associated mitral valve disease. *Circulation*, 9: 552, 1955.
19. Miller, G., Goldberg, H., Elisberg, E., Snider, G., Toor, H. and Katz, L. N. Cardiopulmonary studies in patients with mitral stenosis. I. Circulatory dynamics. *J. Lab. & Clin. Med.*, 40: 390, 1952.
20. Goldberg, H., Bakst, A. A. and Bailey, C. P. The dynamics of aortic valvular disease. *Am. Heart J.*, 47: 527, 1955.

Postcardiotomy Syndrome in Patients with Rheumatic Heart Disease*

Cortisone as a Prophylactic and Therapeutic Agent

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THE efficacy of mitral valvuloplasty in rheumatic heart disease, both in improving the patients clinically and in favorably altering the cardiovascular hemodynamics, is adequately confirmed by many reports.[1–9] However, a complication with very low mortality but nonetheless capable of increasing morbidity, delaying convalescence, increasing duration of hospitalization and frequently incapacitating the patient at variable periods after surgery, has been observed.[5,7,9–15] This complication has been variably called "postcommissurotomy syndrome,"[15] "reactivation of rheumatic fever following mitral commissurotomy"[11] and "postvalvulotomy syndrome."[14] Mitral commissurotomy does not, however, appear to be necessary for the development of this syndrome, since this postoperative complication developed in one of our patients in whom no mitral valve surgery could be performed because of technical difficulties during cardiotomy. Elster[15] reported the occurrence of this syndrome in a patient with rheumatic heart disease in whom only a pericardiotomy was performed. It would seem, therefore, that the title "postcommissurotomy syndrome," although applicable to the majority of cases, is a misnomer. Perhaps the designation "postcardiotomy syndrome in patients with rheumatic heart disease" would be more suitable. As greater insight into the etiology and pathogenesis of this syndrome is achieved, a more satisfactory title may be devised.

The postcardiotomy syndrome is characterized by the following clinical features, in descending order of frequency: Fever, chest pain of a pleuropericardial nature, congestive heart failure, pleural effusion, polyarthritis, arrhythmia, abdominal pain and subcutaneous nodules. (Table I.) A few instances of hemoptysis[11,15] and psychosis[11] have been reported. Laboratory evidence for a non-specific inflammatory process is frequently present. An elevated antistreptolysin-O titer is only rarely present and, when it is elevated, only minimally so. Bacteriologic studies have not revealed any consistent pattern; in our studies the beta hemolytic streptococcus has not been isolated from cultures of the nose and throat, pleural fluid, urine, blood or sputum. Death has occurred infrequently. The syndrome appears postoperatively after a variable latent period from the immediate postoperative period to seventeen months. The majority of initial episodes occur within one month after surgery.

Reports have been made concerning the use of salicylates,[5,7,11,13,15,16] pyramidon[16] and antibiotics[5,7,15] with variable effects on the incidence, duration and intensity of the clinical manifestations of this syndrome. (Table II.) To date, there have been only two cases reported in the literature in which cortisone and ACTH have been used.[11] The authors have had the opportunity to observe a large number of patients who have had this syndrome and who were treated with various therapeutic agents, predominantly cortisone. Cortisone was used during the immediate postoperative period after difficulties were encountered in treating the syndrome with the other agents mentioned and it was instituted

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TABLE I
FREQUENCY OF MANIFESTATIONS OF POSTCARDIOTOMY SYNDROME (PCS) IN PATIENTS WITH RHEUMATIC HEART DISEASE IN CONTROL GROUP AND IN GROUP II

Incidence of PCS	Group I			Group II		
	Total of 12 Patients (46%) with 54 Episodes			Total of 21 Patients (36%) * with 69 Episodes		
	No. of Patients	Patients with PCS (%)	No. of Episodes	No. of Patients	Patients with PCS (%)	No. of Episodes
Fever	12	100	54	21	100	69
Chest pain	10	83	47	19	90	60
Congestive heart failure	7	58	13	3	14	7
Pleural effusion: †						
Left	5	42	6	3	14	3
Bilateral	1	8	1	1	5	1
Arthritis	3	25	4	3	14	4
Arrhythmia	2	17	4	2	10	3
Pneumonitis	2	17	4	..	...	..
Abdominal pain	2	17	2	..	...	..
Pericardial effusion	..	...	..	1	5	1
Subcutaneous nodules	1	8	1	..	...	..

* During and after cortisone administration.
† Occurring after the third postoperative week.

immediately after surgery as a prophylactic agent in all cases undergoing mitral valvuloplasty from 1952 to 1955, when not contraindicated.

It is the purpose of this report to add to the information available concerning this syndrome, to give the results of the use of prophylactic cortisone in a large group of patients with rheumatic heart disease undergoing cardiotomy for mitral valve surgery, and to evaluate the various therapeutic agents proposed in its treatment.

MATERIALS AND METHODS

Observations were made in eighty-four patients who had undergone mitral valvuloplasty by one of the authors (C. B. R.) from November 1951 to July 1954 and whom we were able to study adequately and to follow-up. Twenty-six were men, ranging in age from twenty-five to fifty (mean thirty-six), and fifty-eight were women, ranging in age from twenty-one to fifty-seven (mean forty-one). Based on the criteria of the New York Heart Association for the classification of functional capacity, there were twelve patients in Class II, sixty-four patients in Class III and eight patients in Class IV. (Table III.) There were fifty-eight patients with "pure" mitral stenosis. Fifteen patients had predominating mitral stenosis but exhibited a complicating grade I to grade II apical systolic murmur with radiation to the axilla but no evidence of left ventricular enlargement. This intensity of apical systolic murmur may be associated either with a roughened anterior mitral leaflet (and no true regurgitation)[17] or with minimal and dynamically nonsignificant mitral insufficiency.[9,18] Surgery did not reveal a mitral regurgitant jet in four of these patients and did disclose a minimal degree of regurgitation in eleven. Eight patients had both mitral stenosis and insufficiency with coexisting minimal left ventricular enlargement. Three patients had predominant mitral insufficiency with some degree of mitral stenosis, left ventricular enlargement and a giant left atrium. The latter three patients were subjected to mitral valvuloplasty because they exhibited a progressively downhill course unaffected by strict medical therapy, including cortisone, and it was hoped that increased mobilization of the mitral valve might result in better functioning of this valve. Patients with aortic valvular lesions were not subjected to surgery if there was any

TABLE II

COMPARISON OF INCIDENCE, MANIFESTATIONS AND TREATMENT OF POSTCARDIOTOMY SYNDROME IN PATIENTS WITH RHEUMATIC HEART DISEASE

(Obtained from Literature and Present Series)

	Janton et al. (1952)	Soloff et al. (1953)	Bercu et al. (1953)	Hurwitt et al. (1953)	January et al. (1954)	Wood et al. (1954)	Julian et al. (1954)	Elster et al. (1954)	Dresdale et al. (1955)
Number of patients	100	179	75	20	63	150	139	16	84
Postcardiotomy syndrome*	30	24	9	40	10	10	6	63	39
Fever†	‖	100	57	¶	100	100	100	95	100
Pleuritic chest pain†	100	100	‖	¶	100	¶	50	100	87
Congestive heart failure†	‖	77	51	‖	¶	‖	‖	18	36
Pleural effusion†	¶	‖	‖	¶	¶	‖	‖	93	35
Arthralgia†	‖	12	29	‖	‖	‖	12	18	20
Arrhythmia†	¶	33	‖	‖	¶	‖	‖	¶	14
Pneumonitis†	‖	‖	‖	‖	‖	‖	‖	‖	17
Abdominal pain†	‖	‖	‖	‖	‖	‖	‖	‖	3
Pericardial effusion†	‖	‖	‖	‖	‖	‖	‖	14	5
Subcutaneous nodules†	‖	‖	‖	‖	‖	‖	‖	‖	2
Psychosis†	‖	9	‖	‖	‖	‖	‖	‖	0
Influenced by salicylates	No	‡	§	‖	‖	No	‖	Yes	No
Influenced by antibiotics	No	‖	‖	‖	‖	No	‖	No	No
Influenced by ACTH or cortisone	‖	?	‖	‖	‖	‖	‖	‖	Yes

* Per cent of total number of patients.
† Per cent of patients with postcardiotomy syndrome.
‡ Occasionally.
§ Slow defervescence after four to twelve weeks.
‖ This symptom not mentioned by the author.
¶ Author stated this was present but no statistics were given.

indication that these defects were hemodynamically significant.

A combined medical and surgical team evaluated the patients preoperatively and followed them postoperatively. History was obtained and physical examination was performed on admission by the house staff and one or more of the authors. Laboratory studies consisted of blood counts, urinalysis, fasting blood sugar, blood urea nitrogen, total protein with albumin-globulin fractionation, antistreptolysin-O titer, erythrocyte sedimentation rate, several blood cultures, chest x-rays with oblique studies including barium swallow, and cardiac fluoroscopy. The patient's rectal temperature was recorded four times a day during the period of observation, and a febrile state was considered to be present if the reading was 100°F. or higher. The usual period of observation preoperatively was 7 to 14 days, during which time the patients were semi-ambulatory unless they were febrile.

Bacterial endocarditis was ruled out by clinical evaluation and blood culture. Three patients had this complication four months to three years prior to surgery but had been treated and were considered to be cured at the time of operation.

Unequivocal clinical evidence for outright rheumatic activity was usually considered a contraindication for surgery. Forty-eight patients were considered to be clinically inactive according to our studies.

TABLE III

ANATOMIC AND FUNCTIONAL CLASSIFICATION OF PATIENTS IN GROUPS I AND II*

Group I (26 cases)		Group II (58 cases)	
Diagnosis and No. of Patients	Class and No. of Patients	Diagnosis and No. of Patients	Class and No. of Patients
Mitral stenosis, 17 Mitral stenosis, mitral insufficiency,† 5 Mitral stenosis, mitral insufficiency, 3 Mitral insufficiency, mitral stenosis‡ 1	II, 2 III, 21 IV, 3	Mitral stenosis, 41 Mitral stenosis, mitral insufficiency,† 10 Mitral stenosis, mitral insufficiency, 5 Mitral insufficiency, mitral stenosis,‡ 2	II, 10 III, 43 IV, 5

* According to the criteria of the New York Heart Association.
† Mitral insufficiency of minor degree.
‡ Mitral stenosis of minor degree.

Thirty-four of the eighty-four patients, although not showing evidence clinically of rheumatic activity, did have either a period of low grade fever or laboratory test abnormalities. (Table IV.) Two patients who were thought to have tight mitral stenosis manifested preoperative evidence consistent with some degree of rheumatic activity. These patients were operated on at a time when our concepts concerning the significance of mild rheumatic activity as a contraindication

TABLE IV

CORRELATION OF PREOPERATIVE CLINICAL AND LABORATORY DATA AS RELATED TO DEVELOPMENT OF POSTCARDIOTOMY SYNDROME (PCS) IN PATIENTS WITH RHEUMATIC HEART DISEASE

	Group I (26 cases)		Group II (58 cases)	
	No. with PCS	No. without PCS	No. with PCS	No. without PCS
History of acute rheumatic fever	4 (33%)	8 (67%)	13 (42%)	18 (58%)
History of exertional chest pain*	3 (37%)	5 (63%)	2 (33%)	4 (67%)
History of emboli	4 (67%)	2 (33%)	6 (33%)	12 (67%)
Recent rapid cardiac deterioration	1 (50%)	1 (50%)	6 (36%)	1 (14%)
History of low grade fever	4 (40%)	6 (60%)	10 (35%)	19 (65%)
Leukocytosis	3 (75%)	1 (25%)	11 (39%)	17 (61%)
Elevated erythrocyte sedimentation rate	4 (57%)	7 (43%)	11 (42%)	15 (58%)
Elevated antistreptolysin titer	2 (100%)	0	2 (40%)	3 (60%)
Hyperglobulinemia	1 (33%)	2 (67%)	2 (33%)	4 (67%)
Aschoff bodies†	1 (33%)	2 (67%)	2 (29%)	5 (71%)

* This pain does not resemble the pleuritic type seen in the postcardiotomy syndrome.
† As found in auricular appendage at operation.

for surgery in the presence of a tight mitral stenosis were changing because of our results with postoperative cortisone.

Thoracotomy and cardiotomy were performed on one patient but mitral commissurotomy could not be accomplished because of a small, extremely friable auricular appendage. Two patients died after surgery. One patient died on the operating table of hemorrhage from a friable auricular appendage. The other patient died sixteen days postoperatively due to sudden onset of uncontrollable pulmonary edema. The latter patient will be described in more detail later. Biopsy specimen of the left auricular appendage was taken in all patients on whom surgery was performed.

All patients were closely observed postoperatively for recrudescence of rheumatic fever, chest pain, rise in temperature, pleurisy, pleural effusion (especially in the right chest), arrhythmias, infectious processes, polyarthritis and deterioration of cardiac status. Laboratory studies similar to those done preoperatively were obtained after surgery. The postoperative hospital stay varied from eleven to 161 days (average twenty-one days).

For the purpose of study of the prophylactic use of cortisone postoperatively the patients were subdivided into two groups. Group I, which consisted of twenty-six patients, serves as the control group. The patients of this group did not receive cortisone prophylactically during the immediate postoperative period. The majority of these patients were among the first at this hospital to undergo mitral commissurotomy before 1952. When patients in this group developed the postcardiotomy syndrome they were treated with salicylates, pyramidon, antibiotics, cortisone or ACTH. Group II consisted of fifty-eight patients who received cortisone as prophylactic therapy within the first two postoperative days and who were maintained on cortisone for three to eight weeks thereafter. Dosages for prophylactic cortisone ranged from 150 to 300 mg. daily for the first two weeks and 75 to 150 mg. for the next one to six weeks. Patients receiving prophylactic cortisone were sent home or to a convalescent home on an ambulatory basis after being discharged from the hospital. They then returned to the hospital for cortisone withdrawal, at which time they received ACTH-gel (40 to 80 units daily) for five to seven days. Cortisone dosage was reduced during the first three days of ACTH and then stopped. In our more recent cases, not reported herein, it has been found that ACTH given over a period of not less than fourteen days, eleven days after cortisone was stopped, gave a lower incidence of recrudescence of the postcardiotomy syndrome.

All the patients in Group II after the period of prophylactic cortisone and all the patients in Group I during the entire period of observation were used in this study for evaluation of the efficacy of the various therapeutic agents including cortisone.

The known contraindications for the use of cortisone, for example, tuberculosis (active or inactive), peptic ulcer, psychic disturbances, hypertension, infectious diseases and diabetes, were sought for but not found in any of the patients. A history of bacterial endocarditis was not considered a contraindication, since a cure was present at the time of surgery. Cortisone was used in the presence of congestive heart failure without deleterious effects.[19]

The distribution of patients with regard to anatomic diagnosis and functional cardiac classification (according to the criteria of the New York Heart Association) was essentially similar in Groups I and II. (Table III.) No significant difference was noted in the number of

TABLE V

CORRELATION BETWEEN ANATOMIC AND FUNCTIONAL CARDIAC CLASSIFICATION* AND DEVELOPMENT OF POSTCARDIOTOMY SYNDROME IN PATIENTS WITH RHEUMATIC HEART DISEASE

	Preoperative		Postoperative	
	Group I (12 cases) (No. of patients)	Group II (21 cases) (No. of patients)	Group I (No. of patients)	Group II (No. of patients)
Class:				
I	0	0	6	13
II	1	3	5	5
III	9	16	1	3
IV	2	2	..	..
Diagnosis:				
Mitral stenosis	8	17		
Mitral stenosis, mitral insufficiency†	2	1		
Mitral stenosis, mitral insufficiency	1	2		
Mitral insufficiency, mitral stenosis‡	1	1		

* According to the criteria of the New York Heart Association.
† Mitral insufficiency of minor degree.
‡ Mitral stenosis of minor degree.

patients who had inactive rheumatic heart disease or in those who had equivocal evidence of minimal degrees of rheumatic activity preoperatively in both groups. (Table IV.) The number of patients with a history of rheumatic fever was similar in both groups.

RESULTS

Eight (31 per cent) of the twenty-six patients in Group I who did not receive cortisone prophylactically during the immediate postoperative period exhibited the postcardiotomy syndrome during the initial three to eight weeks after surgery. In four (7 per cent) of the fifty-eight patients in Group II who received cortisone immediately after operation and for three to eight weeks thereafter the syndrome developed during a similar period while taking prophylactic cortisone. The incidence of the postcardiotomy syndrome, however, was similar in both groups (31 per cent in Group I and 29 per cent in Group II) after this initial postoperative period of three to eight weeks when cortisone was discontinued in Group II.

Table IV summarizes various preoperative data on patients in both groups in whom the syndrome did or did not develop. This analysis was made in order to determine if it were possible to predict in which of the patients with rheumatic heart disease the postcardiotomy syndrome would develop after surgery. The ages of the thirty-three patients who had the syndrome varied from twenty-one to fifty-seven years. Fifteen patients (45 per cent) were from thirty-six to forty-five years of age. The preoperative and postoperative anatomic and functional cardiac classifications were not factors in the development of the postcardiotomy syndrome. (Table V.) The incidence of a history of acute rheumatic fever in those patients who had the postcardiotomy syndrome was essentially similar to those patients in whom the syndrome did not

TABLE VI

POSTCARDIOTOMY SYNDROME IN GROUP II (36 PER CENT)
Relation to Cortisone Administration

	No. of Patients	Patients with Post-cardiotomy Syndrome (%)
Reduced dosage	4	19
Within one week after cortisone withdrawal	11	52
One month or more after cortisone withdrawal	6	29

TABLE VII

NUMBER OF PATIENTS AND EPISODES WITH POSTCARDIOTOMY SYNDROME IN GROUPS I AND II TREATED WITH SALICYLATES, PYRAMIDON, ANTIBIOTICS AND CORTISONE

	Group I				Group II				Results
	Fever		Pain		Fever		Pain		
	No. of Patients	No. of Episodes	No. of Patients	No. of Episodes	No. of Patients	No. of Episodes	No. of Patients	No. of Episodes	
Untreated	3	5	3	5	...	..	...	..	.....
Salicylates	8	17	6	18	14	21	13	19	Comparable to patients untreated
Pyramidon	4	4	4	4	3	3	3	3	Comparable to patients untreated
Antibiotics	9	10	6	6	3	3	1	1	No response
ACTH	1	1	1	1	...	..	...	..	Dramatic and rapid remission of symptoms
Cortisone	7*	27	6†	22	14‡	38	13§	37	Dramatic and rapid remission of symptoms

* Five of these patients previously received salicylates and two received pyramidon.
† Four of these patients previously received salicylates and two received pyramidon.
‡ Six of these patients previously received salicylates and one received pyramidon.
§ Six of these patients previously received salicylates and one received pyramidon.

TABLE VIII

POSTCARDIOTOMY SYNDROME IN PATIENTS WITH RHEUMATIC HEART DISEASE

Time and Occurrence After Surgery	Group I (26 cases)	Group II (58 cases)
Three to eight weeks	8 (31%)	4 (7%)
Three to twenty-four weeks	8 (31%)	17 (29%)

develop. Of those patients in both groups in whom the postcardiotomy syndrome developed, seventeen (52 per cent) had a past history of rheumatic fever. The number of patients giving a history of exertional chest pain, of embolization and of recent deterioration in cardiac status is too small for significant conclusions. Review of the data of those having preoperative equivocal evidence of rheumatic activity (as manifested by periods of low grade fever and/or laboratory test abnormalities) again indicates that there is no correlation with the development of the postcardiotomy syndrome. Sixteen (48 per cent) of those patients in both groups who had the postcardiotomy syndrome had equivocal evidence of minimal preoperative rheumatic activity. Similarly, the presence of Aschoff bodies in the auricular appendages at the time of surgery is of no significance in this regard. Two patients in our series, one in each group, had some degree of clinical rheumatic activity just prior to surgery. In one patient the postcardiotomy syndrome developed eight days and again sixteen days after surgery and the other four months after surgery. Although this number is too small to be significant, the experience of the authors suggests that as more surgery is performed on patients who do have clinical rheumatic activity the incidence of the postcardiotomy syndrome probably will increase.

When the postcardiotomy syndrome developed in our patients the symptoms, physical findings and laboratory data were similar in both groups.

An analysis of each feature of the syndrome, as observed in these patients, follows:

Fever. Usually an abrupt rise in temperature occurred to a peak of 101° to 102°F. and occasionally to as high as 103° to 104°F. at the onset of the postcardiotomy syndrome. In a smaller number of patients a gradual rise in temperature occurred over a period of several days.

All patients (eighty-four) in this series were febrile during the immediate postoperative

period. Cortisone given prophylactically, as in Group II, had no significant effect on this fever which lasted three to seven days in the patients in each group with an average of four and a half days in Group I and four days in Group II. However, six patients in Group I and three patients in Group II did not conform to this pattern. Fever in these patients persisted for as long as nine to forty days postoperatively, with no apparent surgical complications. Eight of these patients had recurrences of fever in association with other stigmas of the postcardiotomy syndrome at some later date.

All thirty-three patients (100 per cent) in whom the syndrome developed had elevations in temperature during the 124 episodes observed. Eight of the twelve patients in Group I in whom the postcardiotomy syndrome developed had an attack of fever as the first manifestation of the syndrome at periods varying from the immediate postoperative period to five weeks after surgery. In two other patients the initial episode of fever developed after a latent period of five to seven months, in one patient after fifteen months and in another patient after seventeen months. Ten of the twelve patients had a total of twenty-five febrile episodes. Of these, twelve episodes occurred within the first three months postoperatively, seven from four to seven months, four between ten to fifteen months, one at the seventeenth month and one at the twenty-eighth month. One patient exhibited ten episodes between the fifteenth and twenty-fourth postoperative months, and another patient twenty episodes between the fifth week and twenty-fourth month.

Four (19 per cent) of the twenty-one patients in Group II who developed the postcardiotomy syndrome had eight episodes of fever during the initial three to eight weeks after surgery while receiving cortisone prophylactically. In three patients fever of 101 to 103°F. occurred while they were receiving 75 to 100 mg. of cortisone daily. Increasing the dose to 150 mg. reduced the temperature to normal within twenty-four to thirty-six hours. In a fourth case fever and pleuropericardial chest pain developed, and the patient died sixteen days postoperatively of acute fulminating pulmonary edema two days after reduction of cortisone from 225 to 150 mg. daily.

In seventeen (81 per cent) of the twenty-one patients in Group II who had the syndrome, febrile episodes developed one to five times per patient for a total of sixty-one episodes after prophylactic cortisone was discontinued. The majority of these episodes occurred between the second and fifth month; occasionally fever recurred up to eleven to twelve months after surgery. In most instances fever would occur as a "rebound phenomenon" (Table VI) within seven days after withdrawal of this steroid but in some patients only after a longer period.

Three patients (Group I) were not in distress during four attacks of fever and therefore were not treated with antibiotics, salicylates, pyramidon or cortisone. The fever gradually subsided in two patients from five to seven days; in the third patient it persisted for three weeks.

Therapeutically, cortisone in doses of 50 to 300 mg. daily was given to twenty-one patients during sixty-five episodes of the syndrome usually because of various coexistent distressing complaints. In sixty-two episodes the fever subsided within twenty-four to thirty-six hours. In three episodes there was no response to 50 to 150 mg. daily. In one of these patients who did not respond to 50 mg. daily, remission occurred dramatically with 200 mg. daily ten months later during a second attack. Another patient did not respond to 100 mg. during an attack five months postoperatively but during a later episode 200 mg. daily produced a dramatic remission within twenty-four hours. In several patients fever developed while the subject was receiving small doses of cortisone, that is, 25 to 75 mg. daily. A similar remission occurred upon increasing the dose to 150 mg. The effective dose of cortisone for any single person would then be continued for four to six weeks before withdrawal would again be attempted. Three patients required almost continuous maintenance cortisone therapy for five to twelve months. Every attempt to reduce the dosage would be associated with an exacerbation of symptoms, including fever. With the passage of time it was found that the frequency and duration of the febrile episodes with or without therapy tended to diminish progressively in most patients and that progressively less cortisone was required to achieve a remission. Eventually, in most instances, there were no further recurrences. One patient was given 80 units of ACTH daily, with subsidence of fever within twenty-four hours.

Salicylates in doses of 2.6 to 7.8 gm. daily was given to twenty-two patients during thirty-eight episodes. The temperature gradually declined

from five to seven days, occasionally persisting for as long as two to three weeks, and was essentially as noted in those few patients who did not receive therapy. In some instances the temperature was depressed to 100 to 101° from 102 to 103°F. but then persisted or tended to rise slowly. Eleven of these patients, after failing to respond to this agent during eighteen episodes, were then given cortisone during the same episode. The temperature fell dramatically.

Pyramidon in doses of 2 to 3 gm. daily was given to seven patients, each during one episode. The response resembled that seen with salicylates and in the untreated patients. Two of these patients after failing to respond to this drug were then given cortisone during the same episode. The temperature response was again dramatic.

Antibiotics of all types in adequate doses were given to twelve patients during thirteen episodes. The course of the syndrome was uninfluenced by the agents. (Table VII.)

Chest Pain. Pain characteristic of this syndrome was most frequently located in the left anterior chest where it was also apt to be most severe. It would occasionally radiate to the left axilla, neck, left shoulder, substernum, right anterior chest and back. It was of moderate to marked severity and usually incapacitating. In most instances it was described as being deep-seated and vise-like or constricting, and occasionally as sharp and sticking or dull and aching. The onset was usually abrupt in a patient who was seemingly doing well. The pain was uniformly aggravated by breathing, coughing and, frequently, by the patient being in the prone position. None of the patients in this group complained of pain on swallowing, although we have noted this finding in several of our patients later. A transient pleuropericardial or pericardial friction rub was detected in many instances. The body temperature was found to be elevated during each episode of chest pain. Usually a direct correlation could be noted between the intensity and duration of these two findings.

All patients operated upon had an initial post–thoracotomy incision-type of left chest pain, usually of moderate severity and gradually disappearing from seven to ten days. Cortisone given prophylactically to the patients in Group II neither prevented nor altered this pain.

Twenty-nine (88 per cent) of the thirty-three patients in whom the syndrome developed had pleuropericardial chest pain described during 110 episodes observed. Ten (83 per cent) of the twelve patients in Group I in whom the postcardiotomy syndrome developed had forty-seven episodes of chest pain characteristic of this syndrome. It occurred after a latent period of three to seven weeks in six patients, five to seven months in two patients, fifteen months in one patient and seventeen months in another patient. Eight patients suffered a total of seventeen episodes varying between one to five per patient. Among these, ten episodes occurred from three weeks to six months after surgery, five episodes from seven to twelve months, one at seventeen months and one at twenty-eight months. One patient had ten episodes during the fifteenth to twenty-fourth postoperative months, and another patient had twenty episodes from the fifth week to twenty-fourth month postoperatively.

Two of the twenty-one patients in Group II in whom the syndrome developed manifested pleuropericardial chest pain during the postoperative period of cortisone prophylaxis. In one case this occurred during the fifth week while the patient was receiving 75 mg. daily. Increasing the dosage to 150 mg. daily caused dramatic disappearance of pain within thirty-six hours. In the other patient chest pain occurred eight days postoperatively while he was receiving 150 mg. of cortisone daily. Fever and congestive heart failure were present at the same time. Increasing the dosage of cortisone to 225 mg. produced a dramatic disappearance of symptoms within twenty-four hours. Eight days later, two days after the dosage of cortisone was again reduced to 150 mg., the fever, pleuropericardial chest pain and pulmonary edema recurred. He died of pulmonary edema after eight hours. Additional cortisone instituted early may have reversed the disastrous course as it did during the previous episode.

Seventeen (81 per cent) of the twenty-one patients in Group II in whom the postcardiotomy syndrome developed manifested bouts of pleuropericardial chest pain after the period of prophylactic cortisone. It occurred one to five times per patient for a total of sixty episodes. In many instances the pain appeared as a "rebound phenomenon" within seven days after withdrawal of the steroid. In other patients it occurred after cortisone had been discontinued for a variable period. Most episodes occurred between the second to fifth month, occasionally up to eleven to twelve months after surgery.

Three patients were not treated during four episodes of chest pain because the pain was of moderate severity and did not cause much distress. The pain lasted from five to seven days except in one patient in whom it lasted as long as three weeks.

Therapeutically, cortisone in doses of 50 to 300 mg. daily was given to nineteen patients during fifty-nine episodes of chest pain. Dramatic subsidence of pain occurred within twenty-four to thirty-six hours in fifty-seven episodes. In two episodes there was no response to 50 and 150 mg. of cortisone, respectively. Both of these patients responded rapidly on 200 mg. of cortisone daily during two later bouts of chest pain. This would suggest inadequate dosage during the previous episodes. Several patients developed pain while receiving small doses of cortisone, that is, 25 to 75 mg. daily; remission occurred when the dose was increased to 150 mg. Three patients had to be maintained on practically continuous cortisone therapy for five to twelve months. Every attempt to reduce the dosage was associated with exacerbation of pain. As with fever, it was observed that in most instances progressively less cortisone was required to produce remission. One patient was given 80 units of ACTH; the pain disappeared in twenty-four hours.

Salicylates in doses of 2.6 to 7.8 gm. daily was given to nineteen patients during thirty-seven episodes of chest pain. The pain gradually disappeared after a period of five to seven days, occasionally persisting for as long as two to three weeks, a response resembling that seen in those few patients not treated. Ten of these patients, after failing to respond to salicylates during seventeen episodes, were then given cortisone during the same episode. The pain then disappeared in each instance within twenty-four to thirty-six hours.

Seven patients were given pyramidon, 2 to 3 gm. daily, during one episode each. The response resembled that seen when salicylates were administered. Three of these patients, after failing to respond to this agent, were then given cortisone during the same episode. A striking subsidence of pain occurred within twenty-four to thirty-six hours.

Seven patients were given antibiotics of all types in adequate doses during one episode each of chest pain. No effects attributable to this group of agents were observed.

Arrhythmias. Arrhythmias are grouped according to (1) those occurring in the immediate postoperative period with or without other features of the postcardiotomy syndrome and (2) those occurring at a later date and in association with other features of the syndrome.

In fifty-eight patients (69 per cent) no alterations in the preoperative cardiac rhythm developed postoperatively. Fifty-three of these patients were receiving maintenance digitalis prior to surgery. Thirteen patients had regular sinus rhythm. In eighteen (31 per cent) of these fifty-eight patients (seven patients in Group I and eleven patients in Group II) attacks of the postcardiotomy syndrome later developed.

Twenty-six patients (31 per cent) exhibited abnormal cardiac rhythms in the immediate postoperative period. Of this number, eight patients were in Group I (31 per cent) and eighteen patients were in Group II (31 per cent). Twenty-one (89 per cent) of these twenty-six patients had regular sinus rhythm prior to surgery and twenty-two episodes of auricular fibrillation developed from the first to eleventh postoperative day. Fourteen of these twenty-one patients were receiving maintenance dosage of a digitalis preparation prior to surgery. Conversion to regular sinus rhythm, attempted in fourteen patients by the use of quinidine, was successful in twelve patients. Five patients, all in Group II, reverted spontaneously. No attempts at conversion were made in two patients. An essentially similar incidence was noted in both groups of those patients with preoperative regular sinus rhythm in whom auricular fibrillation developed postoperatively, of those receiving digitalis therapy, and of those in whom conversion to regular sinus rhythm was successful. Conversion to regular sinus rhythm with the use of quinidine occurred with greater ease if attempted during the second postoperative week in either group. Less quinidine was required and a lower incidence of quinidine toxicity occurred. Relatively less digitalis was required to reduce the ventricular rate below 100 during the first postoperative week in those patients of Group II in whom auricular fibrillation developed. Twelve (57 per cent) of these twenty-one patients later manifested attacks of the postcardiotomy syndrome. These included four of the five patients in Group I and eight of the sixteen patients in Group II.

In the remaining five of the twenty-six patients arrhythmias of other types developed from the first to tenth postoperative days. Three were

in Group I and two in Group II. Three manifested multiple premature ventricular contractions and one supraventricular tachycardia. Another patient who had a nodal rhythm prior to operation developed auricular fibrillation. These were readily controlled with digitalis, quinidine or pronestyl® when indicated. All patients except one with multiple premature ventricular contractions had been receiving digitalis in maintenance dosage prior to surgery. Three of these five patients, one in Group I and two in Group II, later exhibited the postcardiotomy syndrome.

One patient in Group I had three attacks of paroxysmal auricular fibrillation from one to four months after surgery. These episodes were associated with other features of the syndrome, including pneumonitis. Salicylates and quinidine were given during the first episode. When she failed to improve, cortisone was given in place of salicylates. A dramatic improvement occurred in the respiratory symptoms, and reversion of auricular fibrillation to regular sinus rhythm was noted. Cortisone and quinidine were given during the other two episodes, and good response of the respiratory complaints and easy reversion to regular sinus rhythm resulted on each occasion.

In one patient in Group II in whom the syndrome developed three weeks postoperatively and who had a regular sinus rhythm, auricular fibrillation developed several months after surgery without symptoms of the postcardiotomy syndrome. Auricular fibrillation had appeared in this patient within the first week after surgery, and conversion at that time with quinidine was successful.

Congestive Heart Failure. This feature is subdivided according to (1) those cases occurring in the immediate postoperative period with or without other features of the syndrome and (2) those occurring at a later date and in association with other features of the syndrome.

Four of the twenty-six patients in Group I and three of the fifty-eight patients in Group II had one episode each of acute pulmonary edema from the first to eighth day after surgery. Six of these patients had been receiving maintenance digitalis prior to surgery. Six episodes were associated with the onset of auricular fibrillation and one with the appearance of paroxysmal supraventricular tachycardia. All were readily controlled with routine cardiac measures and cortisone. In one of these patients, as already described, another episode of acute pulmonary edema developed on the sixteenth day and the patient died in this state. Attacks of fever and pleuropericardial chest pain developed at later dates in the other six patients.

In ten patients, including seven in Group I and three in Group II, evidence of congestive heart failure later developed during sixteen episodes of the syndrome. Fever was present during all sixteen episodes, chest pain in eight and joint pains in three. All patients had been receiving maintenance doses of digitalis. Thirteen episodes occurred in Group I, eight between the third week and fifth month and five between the tenth and eighteenth month after surgery. Two patients of the three in Group II exhibited cardiac decompensation five and six weeks postoperatively after cortisone prophylaxis had been withdrawn. All patients were following a strict cardiac regimen. Because of various coexistent distressing complaints, cortisone, 50 to 300 mg. daily, was given at the same time during nine episodes. Improvement in cardiac status occurred within forty-eight to seventy-two hours. Although disappearance of the chest pain and fever could be attributed to the effectiveness of cortisone, it is difficult to ascertain the effect of the steroid in this group because other cardiac measures were intensively administered at the same time. However, it was noted in one patient that the addition of cortisone to other therapeutic cardiac measures produced a dramatic improvement in the general condition, specifically in pneumonitis, heart failure, high fever and uncontrollable ventricular rate, in spite of full digitalis therapy plus salicylates or pyramidon in adequate doses. The third of the three patients in Group II manifested attacks of fever and mild pulmonary congestion intermittently from the first week to the time of this writing, ten months after surgery. Cortisone in varying doses reduced the temperature to normal limits within twenty-four hours and corrected the complaints referable to mild pulmonary congestion within forty-eight hours. It is of interest that this patient was extremely sensitive to digitalis. Small doses of any of the several different preparations tried produced ventricular bigeminy.

No obvious evidence was noted of the usual factors precipitating acute congestive failure, namely, the patient neglecting to follow the given medical regimen, acute periods of stress (trauma, infections, emotional factors), ar-

rhythmias, myocardial infarction or pulmonary emboli.

Joint Pains. Six (18 per cent) of the thirty-three patients in whom the syndrome developed exhibited polyarthralgias of a non-migratory type. Fingers, wrists, elbows, ankles and knees were involved. No swelling, redness or warmth occurred. Three patients were in each group. The three patients in Group I had four attacks of mild to moderate polyarthralgias from three weeks to seventeen months after surgery. In none of the patients in Group II did polyarthritis develop while the patient was receiving prophylactic cortisone. Five of the six patients had six episodes. During five episodes coexisting fever and pleuropericardial chest pain occurred. During three of the six episodes congestive heart failure was also present.

When cortisone was given in doses of 25 to 300 mg. daily during five of the six episodes, the arthralgias disappeared within twenty-four hours in two episodes, within forty-eight hours in one, and after five to six days in two. The sixth patient was given 3.6 gm. aspirin daily, showed no improvement after two days and tinnitus developed. ACTH, 80 units daily, was then substituted for the salicylates. A complete remission occurred forty-eight hours later.

The sixth patient had had practically continuous polyarthralgia of the small and large joints after prophylactic cortisone had been withdrawn; this was frequently associated with periods of low grade fever. The patient had never had joint pains prior to surgery. Salicylate in doses to mild toxicity was never effective in affording relief.

Pleural Effusions. In six of the twenty-six patients in Group I pleural effusions developed during the initial three to eight weeks after surgery. In all instances this was associated with other features of the syndrome. The effusions were left-sided in five patients and bilateral in one. Thoracentesis was required in one patient; unfortunately, this fluid was not analyzed. All six patients received salicylates as well as antibiotics because of coexisting distressing complaints. The pleural fluid remained for many weeks. In two of the fifty-eight patients in Group II pleural effusions developed during the equivalent period postoperatively while the patients were receiving prophylactic cortisone. The effusion was left-sided in one patient and bilateral in the other. Both patients had other features of the postcardiotomy syndrome at the same time. When the dosage of cortisone was increased, remission of coexistent fever and chest pain occurred but the pleural fluid persisted for many weeks.

In five patients, three in Group I and two in Group II, left-sided pleural effusions developed after the initial postoperative three to eight weeks. These occurred from five weeks to ten months after surgery. Thoracentesis was required in one case. All had other features of the syndrome at the same time. Cortisone was given in doses of 50 to 300 mg. daily to all five patients because of coexisting distressing complaints. The fluid remained for many weeks regardless of therapy and frequently long after other stigmas of the syndrome had subsided.

Pericardial Effusions. Three patients in Group II showed roentgenologic evidence of small pericardial effusion. Two of these three patients had pericardial effusions eighteen days and four weeks after surgery while receiving prophylactic cortisone. The third patient had pericardial effusion six months postoperatively while not receiving cortisone. These patients had other stigmas of the syndrome at the same time.

Pneumonitis. Three patients including two in Group I showed roentgenologic evidence of segmental pneumonitis in the left upper lobe in one and in the right lower lobe in two. These occurred at five weeks and fourteen months after surgery in the two patients of Group I and ten months after surgery in the patient in Group II. Fever and chest pain were present at the same time. Two of these patients concurrently had a severe bronchiolitis with pulmonary insufficiency, relieved only by cortisone. The other patient did not respond to 5.4 gm. of salicylate daily for three days and two gm. of aureomycin daily for four weeks.

Abdominal Pain. Two patients had one episode each of abdominal pain four and five months postoperatively. Both patients are in Group I. In the first patient tenderness and rebound tenderness on the right side of the abdomen and "board-like" rigidity in the lower right quadrant was noted. The surgical consultant suspected acute appendicitis. At operation no abnormalities were noted. The appendix appeared normal by gross and microscopic examination. The second case was associated with fever, pleuropericardial chest pain and moderate congestive heart failure. This patient was given large doses of cortisone and antibiotics. The fever and chest

pain disappeared within thirty-six hours and the abdominal pain gradually disappeared within one week without any residua.

In a patient recently seen and not included in this series abdominal pain developed two days after cortisone withdrawal six weeks after surgery. The pain was most severe in the right lower quadrant of the abdomen and was associated with local muscle rigidity and rebound tenderness. Fever, mild pleuropericardial chest pain and leukocytosis also were present. Chest x-rays were negative for pulmonary infiltrations. Acute appendicitis was strongly suspected by the surgical staff. Exploration failed to reveal any abnormality and the appendix was normal. Cortisone was again effective in producing subsidence of fever and chest pain within twenty-four hours and subsidence of abdominal pain within forty-eight hours, although the incisional pain persisted for approximately five days.

Subcutaneous Nodules. One patient in Group I in whom fever, typical type of chest pain, polyarthralgia and congestive heart failure developed four months postoperatively had, at the same time, numerous small subcutaneous nodules predominantly over the abdomen and flank and also over the thorax. These nodules varied in size from a few millimeters to 3 to 4 cm., were firm and discrete, lacked warmth and tenderness, and caused no pain. Erythema was noted over several nodules. A biopsy specimen taken two days after the institution of 2 gm. of pyramidon daily was reported by the pathologist as "granulation tissue, rich in macrophages and polynuclear leukocytes; many eosinophils were also present. A small artery adjacent to the granulation tissue revealed a minimal degree of fibrinoid necrosis with granulation tissue in all coats." The nodule was situated in the subcutaneous tissue. The impression of the pathologist was "subcutaneous granulomatous nodule with minimal panarteritis." Biopsy specimen of a second nodule one week later revealed an "artery in the subcutaneous fat showing an organizing thrombus, fibrinoid necrosis, disruption of the elastica, necrotization of segments of the wall, perivascular granulation tissue and accumulation of inflammatory cells including eosinophilic leukocytes." The impression of the pathologist at that time was "artery as in periarteritis nodosa." The patient had not received any therapy for seven days prior to this latter biopsy. The nodules disappeared after two weeks without additional therapy.

Laboratory Data. Frequent positive findings of a non-specific nature associated with inflammation were noted during the episodes of the syndrome. A mild to moderate leukocytosis, with values as high as 21,000, was usually present. Occasionally, white blood cell counts gave normal results. The leukocytosis tended to recede after three to four weeks regardless of therapy and was frequently present after the remission of other stigmas of the syndrome. The erythrocytic sedimentation rate (Wintrobe method) was also usually elevated, the highest value being 44 mm. per first hour. This tended to follow the leukocytosis but was usually somewhat slower in receding and persisted one to two weeks after the white blood count had returned to normal levels. Cortisone, despite its dramatic effect on the symptomatology, had very little effect on the results of these two laboratory tests. The red blood cell count and hemoglobin values were within normal range.

Hyperglobulinemia was present in one patient of Group I in whom a preoperative value had been normal. The antistreptolysin-O titer was slightly elevated in two patients in Group I, to values of 333 and 250 units per cc., and in one patient of Group II to 333 units per cc. (normal in our laboratory, 200 units per cc. or less). These three patients had other features of the postcardiotomy syndrome at the same time. Bacteriologic studies of the nose and throat, sputum, pleural fluid, urine and blood failed to reveal any consistent pattern; the beta hemolytic streptococcus was never isolated. Electrocardiographic evidence of pericarditis or recent myocardial damage was not seen in any of the patients.

Aschoff nodules were present in the auricular appendages of three patients (9 per cent) who had the syndrome, whereas seven patients (21 per cent) in whom the postcardiotomy syndrome did not develop had Aschoff nodules.

Mortality. Two patients in Group I died following mitral commissurotomy. One patient, who had had several attacks of the syndrome previously, developed eighteen months after surgery (one week prior to admission) severe substernal pain with left arm radiation. She was admitted to another hospital where she signed herself out after two days when the pain disappeared spontaneously. Five days later, upon a recurrence of this pain, she came to the Maimonides Hospital. One-eighth of a grain of morphine was given intravenously because of

severe chest pain. Six minutes later she gasped and died suddenly. Postmortem examination revealed chronic mitral valvular disease, corroborating the antemortem diagnosis of mitral stenosis and insufficiency. All chambers were enlarged, and the viscera showed both chronic and acute congestion. The aortic commissure of the mitral valve was the site of the previous commissurotomy (one year prior to death). The surface at the time of autopsy was smooth and covered by glistening endothelium. No vegetations were present. A mild bilateral adhesive fibrous pleuritis and pericarditis were present. Microscopic study of the heart failed to reveal acute inflammatory changes or Aschoff bodies.

Another patient died two years after surgery due to a mesenteric thrombosis or embolus at a time when no features of the postcardiotomy syndrome were present. This diagnosis was confirmed at abdominal exploration. Autopsy was not obtained in this case.

One death occurred in Group II. This patient died sixteen days after surgery of acute pulmonary edema as described previously under the section on Chest Pain. Autopsy in this patient revealed florid rheumatic myocarditis and endocarditis.

COMMENTS

In our series of eighty-four patients with rheumatic heart disease who underwent cardiac surgery, a syndrome developed in thirty-three patients (39 per cent) which was characterized by fever and (in descending order of frequency) chest pain of a pleuropericardial nature, congestive heart failure, pleural effusion, polyarthritis, arrhythmia, abdominal pain and subcutaneous nodules. Laboratory evidence for a non-specific inflammatory process was frequently present. This increased the immediate postoperative morbidity and also that at a later date, at which time it usually incapacitated the patient. Other groups have reported an incidence of this syndrome varying from 6 per cent[9] to 63 per cent.[15] (Table II.)

Death has occurred on rare occasions. In our series death occurred in two patients while presenting symptoms consistent with the postcardiotomy syndrome. One patient died very shortly after intravenous morphine and the immediate cause of her death was not clear. Autopsy did not reveal any evidence of rheumatic activity. The other patient at autopsy showed florid rheumatic myocarditis. Verheugt[16] at the World Heart Congress in 1954, in his discussion on rheumatic activity after mitral commissurotomy, stated that several deaths occurred in his series in Holland and that none of these showed evidence of rheumatic activity at necropsy. Soloff et al.[11] report three deaths in their series of cases; the patients died of congestive heart failure. Autopsy in one case revealed rheumatic myocarditis.

A comparison of the results in the authors' control group of patients (Group I) with those in the group who received prophylactic cortisone for three to eight weeks after surgery (Group II) revealed that the incidence of the postcardiotomy syndrome during the initial postoperative period of prophylactic cortisone is significantly lower in Group II. (Table VIII.) Moreover, when symptoms did occur during this period in this group they were rapidly suppressed by increasing the dose of cortisone. This steroid did not alter the expected post-thoracotomy fever and incision type of chest pain. The average hospital stay after surgery of the patients in Group I was twenty-three days as compared with sixteen days in those patients who received prophylactic cortisone. This difference can be accounted for by the appearance of the postcardiotomy syndrome in the patients in Group I. In this latter group, salicylates, pyramidon and antibiotics did not have any appreciable effect upon the symptoms of the postcardiotomy syndrome. No significant differences were employed in the surgical technic or in the general medical and nursing care of the patients in both groups.

The incidence of the syndrome in both groups was identical after the initial three to eight week postoperative period, when prophylactic cortisone was no longer administered. (Table VIII.) This would indicate that the natural history of the syndrome was unaltered by steroid therapy.

Cortisone given to those patients in whom the postcardiotomy syndrome developed in both groups produced a rapid disappearance of the symptoms. In doses of 75 to 300 mg. daily, depending upon the person, fever and the pleuropericardial type of chest pain disappeared within twenty-four to thirty-six hours. Joint pains usually disappeared within forty-eight hours after institution of cortisone therapy, occasionally lasting as long as five to six days. Abdominal pain in one patient who received cortisone disappeared after one week. Later a patient not included in this series responded

with dramatic disappearance of abdominal pain within twenty-four hours after institution of cortisone therapy.

It is more difficult to evaluate the effects of steroid therapy in those patients who had suffered deterioration in the cardiac status (associated with other signs of the postcardiotomy syndrome) because these patients received intensive cardiac therapy at the same time. However, the addition of cortisone to other cardiac measures in one patient produced a marked improvement in the patient's general condition as well as a dramatic effect upon the heart failure which could not be controlled by a strict cardiac regimen plus salicylates or pyramidon. The one patient mentioned in detail in the section on Chest Pain, who died with features of the syndrome and acute pulmonary edema after cortisone dosage had been reduced, showed acute rheumatic myocarditis and endocarditis at autopsy. Another patient manifested attacks of fever and mild pulmonary congestion intermittently from the sixth week to the present writing, ten months after surgical intervention. Cortisone in varying doses reduced the temperature to normal within twenty-four hours and corrected complaints referable to pulmonary congestion within forty-eight hours. This patient was shown to be extremely sensitive to digitalis, suggesting the presence of myocarditis.

Although pathologic evidence for the existence of myocarditis in this syndrome is not conclusive, its presence is suggested by occasional deterioration in cardiac function in patients with pure mitral stenosis who have had satisfactory mitral commissurotomies and in whom no other reason for cardiac deterioration can be found. Cortisone and ACTH have been demonstrated to have a favorable effect in some patients with myocarditis,[22–27] and this might well be the reason for the apparent effectiveness of cortisone in these cases. Cortisone also appears to have a favorable clinical effect on patients with clinically inactive rheumatic heart disease, severe pulmonary congestion and right heart failure either before or after mitral valve surgery.[28] The patients become more comfortable, have less dyspnea and orthopnea, do not gain weight as rapidly as prior to cortisone administration, and require less mercurial diuretics. Moreover, the ventricular rate in patients with auricular fibrillation seems to be more easily controlled with digitalis preparations. Significant hemodynamic changes were not found in some of these patients who underwent studies utilizing the technic of right heart catheterization before and during administration of cortisone.[19] Similarly, Schemm and Camara[20,21] have observed favorable effects of corticotropin in patients with congestive heart failure of various etiologies. They indicate that cortisone produced a sodium and water diuresis or else increased the response to mercurial diuretics when refractoriness previously was present. Further study is required to determine the effects of steroids in heart disease and heart failure.

Adequate evaluation of the effects of cortisone on pleural and pericardial effusions could not be made because many of the patients left the hospital when they became asymptomatic. No significant differences in the laboratory findings were noted between those in Group I and II.

ACTH had an effect similar to that of cortisone upon the symptoms of the postcardiotomy syndrome. Antibiotics did not appear to be of value in the prophylaxis or treatment of this disease. Salicylates and pyramidon in adequate doses have been given to many patients during episodes of the syndrome. The course of the patients who received these two "antirheumatic" agents resembled that of untreated patients. The symptoms gradually disappeared over five to seven days, occasionally persisting for as long as three weeks. In no instance was there as rapid and as striking a disappearance of symptoms as was seen in patients given cortisone. This was demonstrated repeatedly when different patients were compared as well as when the same patient was given different agents either during a single episode or during different episodes of the syndrome. A review of the literature describing the effects of salicylates used for this disease reveals a pattern of response similar to that seen in our patients, that is, gradual disappearance of the symptoms or no effect at all.[5,7,13,16] On the other hand Elster[15] reported favorable response to salicylates.

No undesirable side reactions were noted in those patients who received cortisone. No hypertension, diabetes, peptic ulceration, infections or aggravation of congestive heart failure was seen.

Because of the possibility that the etiology of this disease involves a hypersensitivity phenomenon (to be described in more detail subsequently), benadryl,® 50 mg. every six hours, was given to two of our patients who were seen later

and not included in the present report. No significant response to this agent was noted.

Our results indicate that cortisone did not prevent the appearance of arrhythmia in the immediate postoperative period. However, clinically it has been our impression that the ventricular response to auricular fibrillation is more easily controlled with digitalis to rates below 100 when the patient is concomitantly receiving cortisone. The incidence of conversion of auricular fibrillation to regular sinus rhythm did not seem to be affected by cortisone.

No correlation was found between any one or more preoperative clinical or laboratory findings and the development of the syndrome which would enable one to determine in which patient the syndrome might develop. However, it seems that those patients who have overt signs of rheumatic activity are more prone to develop the syndrome after cardiotomy.

The cause of this syndrome remains obscure. Others have incriminated multiple pulmonary emboli.[12] We do not concur. Although the chest pain is pleuritic in nature and pleural effusions do occur, there was in our patients no hemoptysis, no electrocardiographic evidence of acute cor pulmonale, and no roentgenologic evidence of areas of atelectasis or infiltration other than an occasional segmental pneumonitis. Furthermore, it would be difficult to explain other findings such as polyarthralgia, lower abdominal pain and pericardial friction rubs on this basis. The striking response to cortisone therapy and the frequent recurrence of symptoms upon withdrawal of the steroid is certainly not suggestive of pulmonary embolization.

It does not seem likely that clinical or subclinical streptococcal infections are responsible for the production of this disease, either as a direct effect or as a hypersensitivity phenomenon similar to that of acute rheumatic fever. Cultures of the blood, nose and throat sputum, pleural fluid, and urine have not yielded the beta hemolytic streptococcus. In addition, antistreptolysin-O titers have given positive results in only three cases, with values only slightly above normal. Antibiotics, including penicillin, streptomycin and those with broad spectrum activity, have been of no value either as a prophylactic (when given for the initial ten to fourteen days postoperatively) or therapeutic measure. Other investigators have also had this experience.[5,7,15] This is of importance for it has been amply demonstrated, by the work of Rammelkamp and his group[29,30] and by Stollerman,[31] that penicillin, particularly when given early in the course of streptococcal infection, can markedly reduce the incidence of rheumatic fever.

Direct trauma to the intrathoracic structures *per se* in patients without rheumatic heart disease does not produce the postcardiotomy syndrome. A review of the records of 233 patients without rheumatic heart disease undergoing various forms of chest surgery by the same surgeon (C. B. R.) who performed the mitral valve surgery during the same period, did not reveal a symptom complex resembling in any way that described in this report. The procedures included pulmonary resections, excision of mediastinal tumors, correction of various types of congenital heart disease, pericardiectomy, coronary vein ligation, esophagoplasties and thoracic sympathectomies. This has also been the experience of others,[11,15] although Elster et al.[15] report a personal communication from Likoff who observed six cases with manifestations resembling the syndrome which occurred after surgical correction of congenital pulmonic stenosis. Conclusions concerning this latter group must be withheld until more information is available.

In our experience this syndrome has thus far been seen after surgery only in those patients with rheumatic heart disease who have undergone intrathoracic surgical manipulations of the heart. Mitral valve surgery *per se* is not the responsible factor in the cause of this syndrome. Elster[15] observed the occurrence of the syndrome in a patient with mitral stenosis in whom only pericardiotomy was performed. In one of our patients mitral commissurotomy was not responsible for the production of the syndrome since an extremely friable auricular appendage prevented the exploring finger from reaching the mitral valve. Dressler[32] has recently compared the similarities of the syndrome with that occurring in idiopathic recurrent pericarditis. Both of these syndromes have a cyclic type of febrile pleural-pericardial involvement. However, the postcardiotomy syndrome, occurring after surgical trauma to the heart in patients with rheumatic heart disease, may have other manifestations, such as, arthralgia, abdominal pain, psychoses or subcutaneous nodules. The cause of either syndrome has yet to be established, although it has been suggested by Dressler[32] that they are both manifestations of rheumatic fever.

It seems to the authors that the syndrome is related in some way to rheumatic fever, although various differences obviously exist. In rheumatic fever evidence of an antecedent streptococcal infection is usually present, whereas in the postcardiotomy syndrome this is not observed. Symptomatology in rheumatic fever and postcardiotomy syndrome are qualitatively alike but differ strikingly in incidence in some respects. Fever is a frequent and characteristic finding in both groups. Chest pain of a pleuropericardial nature has been a prominent feature in the syndrome, occurring in 87 per cent of our patients. This is in contrast to the reported[15,33] incidence in rheumatic fever which varies from 2.5 to 14 per cent. Conversely, joint symptoms are more prominent in rheumatic fever. Houser et al.[33] reported that polyarthritis was seen in 95 per cent of their patients with acute rheumatic fever. In our series of patients with postcardiotomy syndrome the incidence of polyarthritis was 20 per cent. In addition, the joints involved are less apt to demonstrate inflammatory changes in this latter group.

Other manifestations are seen to a lesser degree in both conditions, for example, congestive heart failure, arrhythmias of various types, abdominal pain, subcutaneous nodules, pleural effusions, pneumonitis and positive non-specific laboratory tests. The antistreptolysin-O titer is usually elevated in acute rheumatic fever, whereas it is usually normal in cases with the postcardiotomy syndrome. Central nervous system complaints were absent in our patients, although others have described psychoses.[7,11] Clinical evidence for endocarditis is lacking in the postcardiotomy syndrome.

The course and natural history of both diseases nevertheless are essentially similar. It is evident that the syndrome is most often characterized by spontaneous remissions and relapses, that is, polycyclic. Occasionally a monocyclic pattern occurs. Data on the pathology of the syndrome are still too scarce to be of any significant value. The relative ineffectiveness of salicylates and pyramidon in the postcardiotomy syndrome is, to be sure, in striking contrast to rheumatic fever. Cortisone and ACTH produce rapid therapeutic remissions in the clinical manifestations in both diseases.

Thus it is suggested that the postcardiotomy syndrome occurs in patients with rheumatic heart disease because of trauma to the heart or pericardium, which has been the site of rheumatic activity at some time in the past. Elster[15] suggested that the inflammatory reaction in which a rheumatic process may be involved develops in response to trauma sustained at the time of surgery and as a reaction to foreign material introduced at that time. Others[11,14,32] also believe that this syndrome may represent rheumatic activity. It would be interesting to know if thoracotomy *per se* in patients with rheumatic heart disease would produce a similar symptom complex. We have been unable to obtain this information which would be extremely helpful in further understanding the pathogenesis of this disease.

That trauma may play a role in precipitating attacks of rheumatic fever has been pointed out by various authors. Bland and Jones in 1935[34] and again in 1952[35] state that attacks of rheumatic fever may follow trauma, surgery, fractures, exposure to cold and non-specific protein shock reactions, for example, typhoid-paratyphoid febrile reactions. Massell and his group[36] discussed the effects of tissue injury in the production of rheumatic lesions. They injected autologous blood into the subcutaneous and deep tissues over the olecranon process and follow this with frictional pressure (rubbing) to that area for ten days thereafter. In 90 per cent of patients with clinically active rheumatic fever, local subcutaneous nodules developed which were clinically and histopathologically indistinguishable from those occurring spontaneously. In 50 per cent of those patients who showed only laboratory evidence of rheumatic activity nodules developed, whereas in only 14 per cent of patients who were inactive by clinical and laboratory criteria did nodules develop. Saline solution was injected into the same areas in some patients; in several of these patients nodules developed. It is interesting in this respect that Soloff et al.[11] have noted masses of red blood cells in the mitral valve beneath the commissurotomy wound in a few patients who died within two weeks after surgery. This group also noted in two patients, who died ten days after surgery, non-specific inflammatory cells suspicious of rheumatic activity in the parietal pericardium along the suture line.

The indications are, therefore, that in a patient who has had rheumatic fever, trauma may play an important role in reactivation of the disease. Patients undergoing surgery for mitral stenosis present a situation analogous to the experiments just cited. In patients with rheu-

matic heart disease, local trauma may well precipitate an exacerbation of existing rheumatic disease. The high incidence of pericardial involvement consequently would be a result of trauma to this structure at the time of surgery. The occasional long latent period that occurs in some patients before symptoms of the postcardiotomy syndrome appear is not readily explainable either on the basis of trauma and/or auto-immunization. Although a latent period of only a few days may occur after trauma before rheumatic fever appears, in no instance has such a long period been described as that which may intervene before the appearance of the postcardiotomy syndrome. If it were only a flare-up of smoldering rheumatic activity, why should it not respond to salicylates or pyramidon as do the symptoms of rheumatic fever? Further study is necessary to explain this latter phenomenon.

It has been our policy since the completion of this study to give ACTH for two days preoperatively and for eight to ten days postoperatively. This regimen has been instituted because of the decreased immediate postoperative morbidity when cortisone was given prophylactically. Cortisone or ACTH has a beneficial effect upon the postcardiotomy syndrome and/or rheumatic myocarditis which can be precipitated in the immediate postoperative period by the trauma of surgery at which time the patient can least tolerate additional stress. If evidence of myocarditis or the postcardiotomy syndrome develops after withdrawal of ACTH or cortisone, then cortisone is given for an extended period of time (four to six weeks) before it is again withdrawn. It has been our experience that ACTH-gel, 60 to 80 units per day, administered for fourteen days during the period of cortisone withdrawal lessens the incidence of the so-called "rebound phenomenon."

SUMMARY

1. The syndrome herein referred to as the postcardiotomy syndrome in patients with rheumatic heart disease was observed in thirty-three (39 per cent) of eighty-four patients with rheumatic heart disease at variable intervals after mitral valvuloplasty. This complication is usually characterized by fever and chest pain of a pleuropericardial nature, occasionally accompanied by congestive heart failure, pleural effusion, polyarthritis, arrhythmia, abdominal pain, and subcutaneous nodules.

2. This syndrome has been variously called "postcommissurotomy syndrome," "reactivation of rheumatic fever following mitral commissurotomy," and "postvalvulotomy syndrome." The designation "postcardiotomy syndrome in patients with rheumatic heart disease" would seem to be preferable because the syndrome was observed in a patient in whom only cardiotomy was performed due to technical difficulties; it would seem, therefore, that mitral commissurotomy is not necessary for its development.

3. Cortisone had a definite suppressive effect on the syndrome. The incidence of postcardiotomy syndrome was 31 per cent in patients not receiving prophylactic cortisone and 7 per cent in the patients in the group receiving hormone prophylaxis. The immediate postoperative course of patients who received prophylactic cortisone was less stormy than that of those who did not. As a therapeutic agent, cortisone was superior to salicylates, pyramidon and antibiotics which did not favorably affect the clinical manifestations of the postcardiotomy syndrome. Cortisone in doses varying from 50 to 300 mg. daily, depending upon the person, caused a dramatic remission of symptoms and fever in the postcardiotomy syndrome.

4. It is recommended that ACTH be given prophylactically for two days preoperatively and for eight to ten days postoperatively in patients undergoing rheumatic mitral valvuloplasty.

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REFERENCES

1. Dexter, L. Pathologic physiology of mitral stenosis and its surgical implications. *Bull. New York Acad. Med.*, 28: 90, 1952.
2. Yu, P. N., Lovejoy, F. W., Jr., Nye, R. E., Jr., Joos, H. A., Beatty, D. C. and Mahoney, E. B. Changes in pressures in the left atrium and pulmonary artery immediately before and after mitral valvuloplasty. *New England J. Med.*, 251: 764, 1954.
3. Munnell, E. R. and Lam, C. R. Cardiodynamic effects of mitral commissurotomy. *Circulation*, 4: 321, 1951.
4. Werko, L., Biorck, G., Crafoord, C., Wulff, H., Krook, H. and Eliasch, H. Pulmonary circulatory dynamics in mitral stenosis before and after commissurotomy. *Am. Heart J.*, 45: 477, 1953.
5. Janton, O. H., Glover, R. P., O'Neill, T. J. E., Gregory, J. E. and Froio, G. F. Results of the surgical treatment for mitral stenosis. *Circulation*, 6: 321, 1952.

6. Ellis, F. H., Jr., Kirklin, J. W., Parker, R. L., Burchell, H. B. and Wood, E. H. Mitral commissurotomy: an overall appraisal of clinical and hemodynamic results. *Arch. Int. Med.*, 94: 774, 1954.
7. Wood, P. An appreciation of mitral stenosis. *Brit. M. J.*, 2: 1113, 1954.
8. Glover, R. P., O'Neill, T. J. E., Harris, J. S. C. and Janton, O. H. The indications for and the results of commissurotomy for mitral stenosis. *J. Thoracic Surg.*, 25: 55, 1953.
9. Julian, O. C., Dye, W. S. and Grove, W. J. Selection of patients for mitral commissurotomy in relation to clinical results. *Arch. Surg.*, 69: 273, 1954.
10. Hurwitt, E. S. The organization of a cardiovascular surgical program: preliminary observations on the surgical treatment of patients with mitral stenosis. *New York State J. Med.*, 53: 1209, 1953.
11. Soloff, L. A., Zatuchni, J., Janton, O. H., O'Neill, T. J. E. and Glover, R. P. Reactivation of rheumatic fever following mitral commissurotomy. *Circulation*, 8: 481, 1953.
12. Bedell, G. N., Culbertson, J. W. and Ehrenhaft, J. L. Management of patients with mitral stenosis before, during and after mitral valvuloplasty. *Arch. Int. Med.*, 94: 718, 1954.
13. Bercu, B. A. A post-operative syndrome following mitral valvuloplasty. *J. Lab. & Clin. Med.*, 42: 783, 1953.
14. January, L. E., Bedell, G. N. and Bateman, R. D. Problem of mitral valve disease. *J. A. M. A.*, 155: 231, 1954.
15. Elster, S. K., Wood, H. F. and Seely, R. D. Clinical and laboratory manifestations of the postcommissurotomy syndrome. *Am. J. Med.*, 17: 826, 1954.
16. Verheugt, A. Personal communication.
17. Janton, O. H., Heidorn, G., Soloff, L. A., O'Neill, T. J. E. and Glover, R. P. The clinical determination of mitral insufficiency when associated with mitral stenosis. *Circulation*, 10: 207, 1954.
18. Zinsser, H. F., Jr. The selection of patients for mitral commissurotomy. *Am. J. Med.*, 17: 804, 1954.
19. Dresdale, D. T., Greene, M. A. and Guzman, S. V. Hemodynamic effects of cortisone in patients with rheumatic heart disease and congestive heart failure. In preparation.
20. Schemm, F. R. and Camara, A. A. The correction of electrolyte deficits in cardiovascular-renal disease. *Circulation*, 10: 430, 1954.
21. Camara, A. A. and Schemm, F. R. Corticotropin (ACTH) in heart disease: its paradoxical effect on sodium excretion in resistant congestive failure. *Circulation*, 11: 702, 1955.
22. Garrison, R. F. and Swisher, R. C. Myocarditis of unknown etiology (Fiedler's?) treated with ACTH. *J. Pediat.*, 42: 591, 1953.
23. Massell, B. H. ACTH and cortisone therapy of rheumatic fever and rheumatic carditis. *New England J. Med.*, 251: 183–190, 221–228, 263–270, 1954.
24. McEwen, C. The treatment of rheumatic fever. *Am. J. Med.*, 17: 794, 1954.
25. Bunim, J. J. The clinical effects of cortisone and ACTH on rheumatic diseases. *Bull. New York Acad. Med.*, 27: 75, 1951.
26. Golden, A. and Hurst, J. W. Alterations of the lesions of acute rheumatic myocarditis during cortisone therapy. *Circulation*, 7: 218, 1953.
27. Kelley, B. C. Corticotropin (ACTH) therapy of initial attacks of acute rheumatic fever in children. *Am. J. Dis. Child.*, 84: 151, 1952.
28. Personal observations.
29. Denny, F. W., Wannamaker, L. W., Brink, W. R., Rammelkamp, C. H., Jr., and Custer, E. A. Prevention of rheumatic fever. *J. A. M. A.*, 143: 151, 1950.
30. Wannamaker, L. W., Rammelkamp, C. H., Jr., Denny, F. W., Brink, W. R., Houser, H. B., Hahn, E. O. and Dingle, J. H. Prophylaxis of acute rheumatic fever. *Am. J. Med.*, 10: 673, 1951.
31. Stollerman, G. H. The prevention of rheumatic fever by the use of antibiotics. *Bull. New York Acad. Med.*, 31: 165, 1955.
32. Dressler, W. Idiopathic recurrent pericarditis: comparison with the postcommissurotomy syndrome, consideration of etiology and treatment. *Am. J. Med.*, 18: 591, 1955.
33. Houser, H. B., Clark, E. J. and Stolzer, B. L. Comparative effects of aspirin, ACTH and cortisone on the acute course of rheumatic fever in young adult males. *Am. J. Med.*, 16: 168, 1954.
34. Bland, E. F. and Jones, T. D. Clinical observations on the events preceding the appearance of rheumatic fever. *J. Clin. Investigation*, 14: 633, 1935.
35. Bland, E. F. and Jones, T. D. The natural history of rheumatic fever. A twenty year perspective. *Ann. Int. Med.*, 37: 1006, 1952.
36. Massell, B. F., Mote, J. R. and Jones, T. D. The artificial induction of subcutaneous nodules in patients with rheumatic fever. *J. Clin. Investigation*, 16: 125, 1937.

Renal Insufficiency, Renal Calculi and Nephrocalcinosis in Sarcoidosis*

Report of Eight Cases

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WITHIN recent years the renal complications of sarcoidosis have received increasing recognition. Alterations in the concentration of serum protein and serum calcium in this disease were first described by Harrell and Fisher[1] in 1939. Several isolated case reports of renal insufficiency in sarcoidosis subsequently appeared.[2,3] Early observers considered that infiltration of renal parenchyma by the granulomatous lesions of sarcoidosis may have been the basis for the impairment of renal function. In a recent review, however, Klatskin and Gordon[4] suggested that renal failure in sarcoidosis might be due to nephrocalcinosis rather than granulomatous infiltration. In a recently reported case[5] of sarcoidosis with renal insufficiency, biopsy of renal tissue showed microscopic evidence of granulomatous infiltration without nephrocalcinosis, and in another case[6] biopsy disclosed very mild chronic pyelonephritis but no characteristic sarcoid lesions or nephrocalcinosis.

In an effort to uncover additional data pertinent to this problem the cases of sarcoidosis with renal complications seen at the Mayo Clinic since 1940 were reviewed. Renal complications, namely, renal insufficiency, renal calculi and nephrocalcinosis, have been encountered in eight cases. The clinical manifestations and the problems in differential diagnosis in these cases form the basis for this report.

CASE REPORTS

CASE 1. A thirty year old white man registered at the Mayo Clinic in October, 1953, with a history of recurrence of renal stones. The first attack of renal colic had occurred in August, 1951. In August, 1952, he had a second attack with subsequent removal of a calcium stone from the left ureter. He estimated that he had passed ten to twelve calculi since August, 1952. In September, 1953, a diagnosis of primary hyperparathyroidism had been made and cervical exploration carried out elsewhere. All four parathyroid glands had been identified and one had been subjected to biopsy. The pathologist reported that only normal parathyroid tissue was present. A mediastinal tumor had been observed on roentgenograms of the thorax as long ago as 1942.

The blood pressure was 110 mm. Hg systolic and 70 diastolic. The results of physical examination were otherwise negative except for scars on the abdomen and left flank. Blood urea measured 58 mg. per 100 cc.; uric acid 4.5 mg. per 100 cc. of serum; serum calcium 12.6 mg. per 100 cc.; serum inorganic phosphorus 2.8 mg. per 100 cc.; plasma chlorides 91.3 mEq./L., carbon dioxide-combining power 22 mEq./L. of plasma; total serum protein 7.3 gm. with 3.9 gm. of albumin and 3.4 gm. of globulin per 100 cc.; and alkaline phosphatase 12.3 King-Armstrong units per 100 cc. of serum. On repetition of tests the serum calcium was 12.2 mg., serum inorganic phosphorus 3.1 mg. and urea 62 mg. per 100 cc. The value for hemoglobin was 10.3 gm. per 100 cc. of blood. The urine had a specific gravity of 1.011 and an acid reaction, exhibited albuminuria, grade 2 (graded on the basis of 1 to 4) and contained numerous erythrocytes and leukocytes. A roentgenogram of the thorax revealed a large tumor of the mediastinum. An excretory urogram disclosed multiple stones in the right renal pelvis and ureter. Roentgenograms of the skull, right hand, right forearm and right leg did not disclose any abnormality. The reaction to the tuberculin skin test was negative. A tentative diagnosis of primary hyperparathyroidism was made. Exploration of the tumor in the upper mediastinum was advised on the chance that it might either contain, or consist of, a parathyroid tumor, perhaps associated with a mediastinal goiter.

Surgical exploration on October 10, 1953, revealed multiple granulomatous masses in the mediastinum

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lying behind the pericardium and in front of the esophagus. They were well encapsulated and were enucleated without disturbance of any of the vital structures. A similar group of nodes was removed from the anterior mediastinum. Microscopic examination disclosed non-caseating granuloma with extensive hyaline changes consistent with a diagnosis of sarcoidosis. Postoperatively, the serum calcium decreased from the previous high levels to 10.6 mg. Urologic surgical procedures were not deemed necessary at this time.

The patient returned in January, 1954, stating that he had been well except for recurrent pain in the right flank. He had passed two stones since dismissal. An excretory urogram revealed multiple small stones in the right renal pelvis and the right ureter. The right pelvis and calyces were dilated. Physical examination disclosed multiple small, firm, discrete nodes in the neck and axillas. Values obtained for serum calcium were 10.2 mg. and 10.5 mg., for serum inorganic phosphorus 2.4 mg. and 3.0 mg., the blood urea was 38 mg. per 100 cc. On February 3, 1954, the renal pelvis was exposed, opened and found to contain numerous, small stones which were removed by lavage. Several calculi were also removed from the right ureter. The postoperative course was uneventful.

In a recent communication the patient informed us that he has continued to pass small stones. Recent studies revealed a value of 11.3 mg. per 100 cc. for serum calcium and 3.5 mg. for serum inorganic phosphorus. A trial of treatment with cortisone has been suggested should the value for serum calcium remain elevated and should additional stones develop.

Case II. A seventy-four year old white man came to the Mayo Clinic in December, 1950, with a chief complaint of generalized pruritus. In 1923 subtotal thyroidectomy had been performed for nodular goiter. In 1937 a diagnosis of nephritis was made and a diet low in salt and protein content was prescribed. At the end of one year on this program he was told that the nephritic condition had improved. Again, in August, 1949, he was told that nephritis was present and was placed on a diet low in salt and protein content. In June, 1950, he was found to have mild anemia which was treated with vitamin B_{12}, liver and iron without significant improvement.

Physical findings included a blood pressure of 150/90, moderate cardiac enlargement, a harsh systolic murmur heard over the apex and aortic area, benign enlargement of the prostate gland and the presence of a left hydrocele and bilateral inguinal hernias. The urine had a specific gravity of 1.010, was alkaline in reaction, exhibited albuminuria, grade 2, and contained a few granular casts and an occasional pus cell. The residual urine in the bladder measured 45 cc. The value for blood hemoglobin was 10.4 gm. and the erythrocyte count was 3,500,000 per cubic millimeter. The blood urea measured 96 mg. and the creatinine 4.8 mg. per 100 cc. A roentgenogram of the thorax did not reveal any abnormality. There was grade 1 narrowing and sclerosis of the retinal arterioles. A diagnosis of chronic diffuse nephritis, probably on a vascular basis, was made. Transurethral resection was advised for relief of obstructive symptoms and, on December 20th, this was performed with uneventful recovery.

The patient returned in June, 1952, complaining of continued generalized pruritus and abnormal fatigue. In the past year several subcutaneous nodules had developed. Excision elsewhere of one of these nodules revealed the presence of calcium deposits. Although no obstructive urinary symptoms were present, the patient had persistent nocturia three or four times during the night.

The blood pressure was 134/88 and the skin was dry. Numerous small cervical, axillary, epitrochlear and inguinal lymph nodes were palpable. The inguinal hernias and hydrocele were unchanged in size. The urine had a specific gravity of 1.008 and exhibited albuminuria, grade 2. The blood hemoglobin measured 10.4 gm. and the serum protein 6.7 gm., with 4.3 gm. of albumin and 2.4 gm. of globulin per 100 cc. The value for blood urea on three occasions was 98, 124 and 118 mg. per 100 cc., respectively, with corresponding values of 6.7, 6.9 and 6.4 mg. for creatinine. The sedimentation rate (Westergren method) was 50 mm. in one hour. The roentgenographic appearance of the right wrist and hand was normal. Roentgenograms of the head presented a normal appearance while a roentgenogram of the thorax revealed only slight torsion of the aorta. A roentgenogram of the kidneys, ureters and bladder revealed a small stone in the upper pole of the left kidney. The serum calcium on three separate determinations measured 11.9, 11.6 and 11.3 mg. per 100 cc. with corresponding values of 5.4, 4.6 and 4.6 mg. for serum inorganic phosphorus. During three days when the patient received a quantitative diet containing 135 mg. of calcium, the urinary excretion of calcium amounted to 288, 259 and 263 mg. in three consecutive twenty-four-hour specimens.

A diagnosis of primary hyperparathyroidism with severe renal damage was considered but biopsy of a lymph node from the epitrochlear region disclosed a non-caseous granuloma histologically compatible with a diagnosis of sarcoidosis. In view of this finding, exploration of the parathyroid glands was not thought advisable since it was realized that sarcoidosis with hypercalcemia could explain all the findings. A diet low in calcium, protein and salt content was prescribed and the patient was dismissed, but he responded poorly; in March, 1953, his home physician prescribed 50 mg. of cortisone acetate daily. The patient has continued to have nodal enlargement and chronic azotemia. Recent studies of the blood revealed that the values for serum calcium and phosphorus were

within normal limits and that the value for non-protein nitrogen was 55 mg.*

CASE III. A thirty-one year old white man was admitted in May, 1942, complaining of shortness of breath with mild exertion. His illness started in February, 1939, when chills, fever and productive cough developed. Since then he had experienced nine similar episodes. Following each episode he became more dyspneic. Enlargement of the liver and spleen had been noted in 1939, at which time he began to have a skin eruption that was confined mainly to his back. Biopsy of one of these skin lesions had been reported to show "Boeck's sarcoid."

Examination revealed a blood pressure of 110/74. No peripheral adenopathy was present. The spleen was markedly enlarged and extended two finger-breadths below the left costal margin. A firm, non-nodular liver was also palpable one to two finger-breadths below the umbilicus. Numerous oval, discrete, pigmented lesions were present over the back, upper part of the arms, and thighs. Biopsy of one of these lesions revealed non-caseous granulomas compatible with a diagnosis of sarcoidosis. A roentgenogram of the thorax revealed diffuse miliary infiltration of both pulmonary fields. The roentgenographic appearance of the hands was normal. The urine had a specific gravity of 1.020 and an alkaline reaction, and it exhibited albuminuria grade 2, pyuria grade 1, and erythruria grade 2 (all on the basis of grade 1 to 4). The serum calcium measured 9.3 mg. and the serum protein 7.8 gm. per 100 cc., with an albumin-globulin ratio of 1 to 1.1 A sulfobromophthalein test of hepatic function showed no retention of dye. The indirect-reacting serum bilirubin measured 1.1 mg. per 100 cc. The sedimentation rate (Westergren method) was 99 mm. in one hour. Repeated examinations of the sputum all gave negative results for tubercle bacilli. Intravenous excretory urography revealed a stone in the lower calyx of the right kidney and probable small stones in the left kidney. The serologic reaction for syphilis was negative. Bronchoscopic examination revealed considerable thick purulent material coming from both main bronchi. Guinea pig studies of this material failed to reveal tubercle bacilli. The patient was dismissed with a diagnosis of generalized sarcoidosis involving the lungs, liver, spleen and skin, and bilateral renal calculi.

The patient died in February, 1950. Postmortem examination revealed sarcoidosis of the skin, lungs, lymph nodes, spleen and liver, and marked cor pulmonale with extensive pulmonary fibrosis and chronic interstitial pneumonitis. Microscopic examination of the kidneys revealed numerous pyelonephritic scars. Calcium deposits were present in some of these scarred areas and also in otherwise normal tissue. The calcium appeared to be located in the interstitial tissue. Collagen fibers and occasionally giant cells were present at the edges of the calcific material. Tiny granulomas composed of fibroblasts, lymphocytes and multinucleated giant cells were observed in all tissue sections. There was no evidence of caseation. (Fig. 1.)*

CASE IV. A thirty year old white man was admitted in September, 1940, complaining of marked fatigue, and exhaustion of two years' duration. A chronic cough had developed in 1939, at which time he was placed in a tuberculosis sanatorium. Studies failed to corroborate a positive diagnosis of pulmonary tuberculosis. However, biopsy of a left inguinal lymph node was reported to show non-caseous tuberculosis. He had no urinary symptoms.

On examination, the blood pressure was 130/70. The tip of the spleen was palpable just below the left costal margin. There were a few moist rales in the bases of both lungs and a scar in the left groin. The ocular fundi appeared normal. Several urinalyses revealed a specific gravity that ranged from 1.008 to 1.013, albuminuria, grade 2, and erythruria, grade 2, in all specimens. The blood urea was 110 mg., the creatinine 5.7 mg., the serum calcium 13.6 mg., the serum inorganic phosphorus 3.9 mg. per 100 cc. The alkaline phosphatase was 1.3 Bodansky units. The sedimentation rate was 125 mm. in one hour. The roentgenographic appearance of the hands and feet was normal. The serum protein measured 8.1 gm. per 100 cc., with an albumin-globulin ratio of 1.3 to 1. The reaction to the tuberculin skin test was negative. Repeated examinations of the sputum gave negative results for tubercle bacilli. A Paunz test for amyloid gave negative results. A roentgenogram of the kidneys, ureters and bladder revealed numerous small areas of calcification in the right kidney. A roentgenogram of the thorax disclosed extensive miliary infiltration that involved both lungs. Tissue sections from the lymph node, removed elsewhere, were re-examined and reported to show non-caseous granulomas. A diagnosis of nephrocalcinosis with renal insufficiency secondary to sarcoidosis was made. A conservative program of adequate rest and fluids with moderate restriction of dietary protein and calcium was outlined. In December, 1952, the patient reported that he was working full time and felt well. No opportunity for follow-up studies has been available.

CASE V. A seventy-two year old white man was admitted in January, 1954, complaining of progressive exertional dyspnea of nine months' duration. There was no associated orthopnea, angina pectoris or edema of the ankles. In June, 1953, the patient had one episode of severe pain in the left flank, which extended into the left testicle. A diagnosis of renal

* Follow-up data kindly supplied by Dr. John A. McLaren.

* Tissue sections kindly forwarded by Dr. E. F. Pearson.

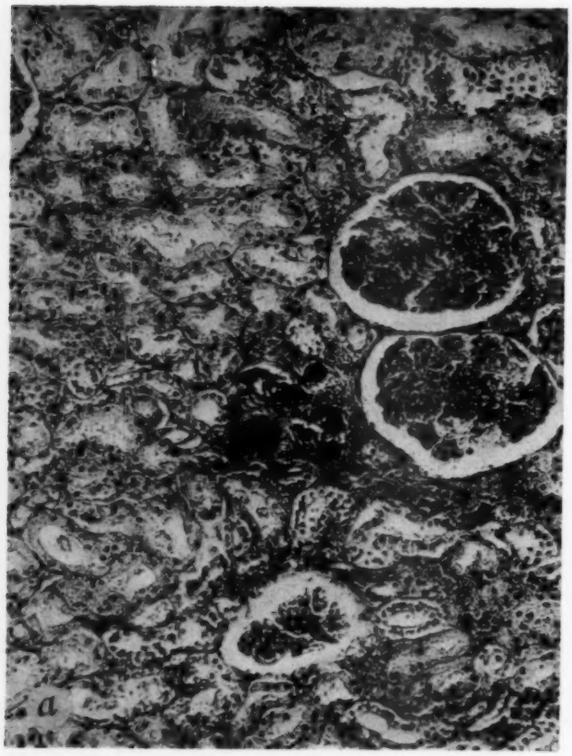

FIG. 1A. Metastatic calcification in the renal parenchyma.

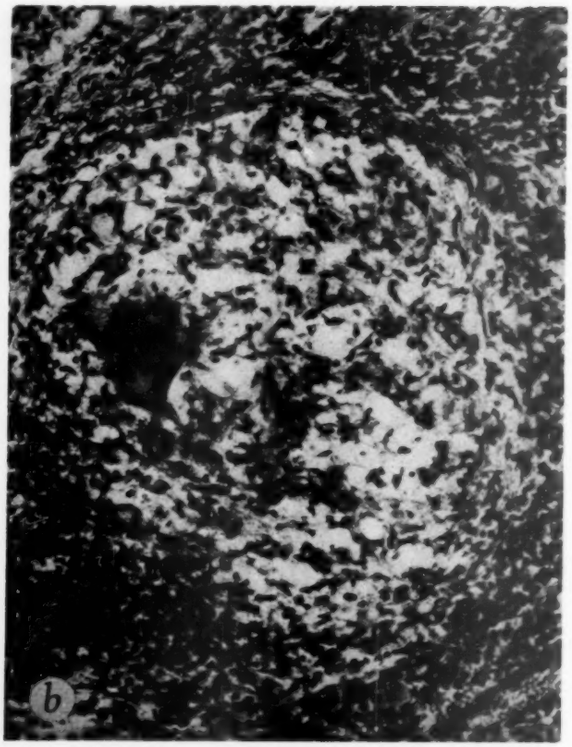

FIG. 1B. Non-caseous granuloma of the kidney.

calculus was considered but never proved. Two months before admission the patient had noted marked polyuria and polydipsia.

On examination, the blood pressure was 120/80. There was scoliosis of the thoracic part of the spinal column with convexity to the right. The lungs were clear to percussion and auscultation. The heart rhythm was regular and no murmurs were audible.

The urine had a specific gravity of 1.007 and an acid reaction, exhibited albuminuria, grade 2, and contained an occasional erythrocyte and leukocyte. The sedimentation rate was 60 mm. in one hour. The value for blood urea was 44 mg., for blood sugar 86 mg., for serum calcium 10.9 mg., for serum inorganic phosphorus 3.8 mg. per 100 cc. The alkaline phosphatase was 7.1 King-Armstrong units. The serum chloride measured 95 mEq. per liter and the carbon dioxide-combining power 25 mEq./L. The concentration of serum protein was 7 gm. per 100 cc., with 3.9 gm. of albumin and 3.1 gm. of globulin. On another occasion the serum calcium measured 10.8 mg. and the serum inorganic phosphorus 4.2 mg. per 100 cc. Roentgenographic examination of the thorax revealed diffuse fibrosis scattered throughout both pulmonary fields. The roentgenographic appearance of the skull was normal. A small polypoid filling defect in the prepyloric segment of the stomach was found on roentgenographic examination. The reaction to the tuberculin skin test was negative, as were the reactions to tests for histoplasmosis and coccidioidomycosis.

When a quantitative diet containing 135 mg. of calcium was given, marked hypercalciuria was observed. The total urinary excretion of calcium on three successive days amounted to 423, 431 and 327 mg., respectively. An excretory urogram revealed several small stones in the calyces of the lower pole of the left kidney and a probable stone in the right renal pelvis.

A diagnosis of primary hyperparathyroidism was seriously considered but in view of the unusual findings in the lungs and a normal value for serum inorganic phosphorus in the absence of marked increase of blood urea, an alternate explanation was sought. When sarcoidosis was considered as a possible diagnosis, the patient was sent to surgery where several lymph nodes were removed from the deep cervical chain on the right side. The pathologist reported that the nodes contained non-caseous granulomas compatible with a diagnosis of sarcoidosis. Studies of pulmonary function revealed findings that were consistent with extensive pulmonary fibrosis. Exploration of the neck was not felt to be warranted since all the clinical and laboratory findings could be attributed to sarcoidosis. Surgical treatment for the gastric polyp was deferred. The patient was instructed to take a diet low in calcium content and was urged to drink an adequate amount of fluids. In

April, 1954, the patient returned because of progressive disabling dyspnea. Otherwise he had felt well, although he still noted polyuria and polydipsia with nocturia (two or three times). The physical findings were unchanged except for a blood pressure of 140/100. The specific gravity of the urine was 1.009, the reaction was alkaline and the albumin content was graded 2. The blood urea measured 34 mg., the serum calcium 9.6 mg. on two occasions, and the serum inorganic phosphorus 3.0 and 2.9 mg. per 100 cc. Roentgenographic examination of the stomach revealed no change in the size of the polypoid lesion. On a diet low in calcium content the patient excreted 309, 120 and 112 mg. of calcium in the urine on three successive days. Because of the progressive dyspnea, a program of oral administration of cortisone under the supervision of the home physician was advised. Subsequent to a full course of this treatment there was decided improvement with respect to exertional dyspnea. The patient has had no subsequent attacks of renal colic. No recent studies of the blood urea or serum calcium have been made.

Case VI. A thirty-three year old white man was admitted in July, 1954, complaining of anorexia, loss of weight and weakness of 6 months' duration. In 1941 routine roentgenographic examination of the thorax had shown hilar infiltration. On the assumption that he had tuberculosis he was placed in a tuberculosis sanatorium for nine months and bedrest was instituted. Laboratory studies, however, failed to confirm this diagnosis. From 1941 through 1945, serial roentgenograms revealed some progression of the pulmonary infiltration. A diagnosis of sarcoidosis was made in 1945 when hypercalcemia and increase of the serum protein with reversal of the albumin-globulin ratio were found. The patient's general health remained good although increased exertional dyspnea developed in 1950 and 1951. He was treated with corticotropin (ACTH) alternating with cortisone from April, 1952, to June, 1953. During this period he gained weight and noticed some improvement in his pulmonary reserve. In June, 1953, periodic episodes of indigestion developed but studies failed to reveal any ulceration of the stomach or duodenum. Since January, 1954, the patient had noted progressive anorexia with loss of fifteen to twenty pounds, generalized weakness, polyuria, polydipsia and nocturia (three or four times). Unexplained gross hematuria was noted in February, 1954, but cystoscopic and renal studies were reported as giving negative results.

On examination, the blood pressure was 104/88. The patient appeared chronically ill and emaciated. Numerous prominent cervical, supraclavicular, axillary and inguinal nodes were palpable. The spleen was moderately enlarged, being palpable 2 finger-breadths below the left costal margin. The urine had a specific gravity of 1.007 and an acid reaction, exhibited albuminuria, grade 2, and contained numerous hyaline and granular casts as well as a few erythrocytes and leukocytes. The sedimentation rate was 60 mm. in one hour. The blood urea measured 98 mg., the creatinine 3.8 mg. and the serum protein 7.4 gm. per 100 cc., with 3.6 gm. of albumin and 3.8 gm. of globulin. The serum calcium measured 14.5 mg. and the serum inorganic phosphorus 3.9 mg. per 100 cc. Roentgenographic appearance of the wrists and hands was normal. Roentgenograms of the thorax revealed diffuse infiltration of the upper two-thirds of both pulmonary fields with considerable enlargement of the hilar shadows. A roentgenogram of the kidneys, ureters and bladder revealed no renal calculi or nephrocalcinosis. The reaction to the tuberculin skin test was negative. Cultures of the sputum and gastric washings were all negative for tubercle bacilli. Biopsy of a lymph node from the left posterior cervical triangle disclosed non-caseating granulomas that were compatible with a diagnosis of sarcoidosis. The only medicine the patient had been taking was in the form of a multiple-vitamin capsule, which contained 1,000 units of vitamin D and which had been taken daily.

The patient was placed on a diet low in protein and calcium content, urged to force fluids, and advised to discontinue use of multiple-vitamin capsules. Three weeks after he returned home he passed a renal stone which was found upon analysis to consist of calcium oxalate.

Three weeks later the blood urea measured 24 mg., the serum calcium 13.6 and 13.2 mg., and the serum inorganic phosphorus 3.2 and 3.3 mg. per 100 cc. The patient had noted some decrease in size of the peripheral lymph nodes, suggestive of a possible spontaneous remission of his disease. He was dismissed on a regimen of high fluid intake and a diet of normal protein but low calcium content. In February, 1955, he reported that his general health was good. Blood studies (elsewhere) in February, 1955, revealed a value of 8.5 mg. per 100 cc. for serum calcium and a value of 9.9 mg. for urea nitrogen.

Case VII. A forty-five year old white man was admitted in February, 1950, complaining of progressive exertional dyspnea, generalized weakness and unexplained anemia of two years' duration. During this interval he had experienced several episodes of low-grade fever associated with generalized weakness. Mild anemia had been discovered in 1948; this had failed to respond to liver, iron or vitamin B_{12} therapy.

On examination, the blood pressure was 120/72. The liver and spleen were greatly enlarged. The urine exhibited albuminuria, grade 2, and erythruria and leukocyturia, grade 3. The value for hemoglobin was 13.4 gm. per 100 cc. of blood, the erythrocytes numbered 4,700,000 and leukocytes numbered 6,200 per cubic millimeter. The value for serum bilirubin was 1.6 mg. per 100 cc., indirect reaction. A liver-function test with sulfobromophthalein revealed

retention of 12 per cent of the dye. A roentgenogram of the thorax disclosed diffuse fibrosis of both pulmonary fields, and an excretory urogram disclosed a calculus in the left kidney. A ninety-six-hour stool specimen contained normal quantities of urobilinogen. The blood urea measured 60 mg., the serum calcium 10.1 mg. and the serum inorganic phosphorus 3.4 mg. per 100 cc. It was believed that the pulmonary findings disclosed on x-ray examination probably represented an occupational fibrosis but the patient denied any exposure to silica or beryllium. Biopsy of the liver revealed a granulomatous hepatitis characterized by the presence of many non-caseous tubercles and consistent with sarcoidosis. The pulmonary findings were then felt to be compatible with changes seen in sarcoidosis. A diet high in carbohydrate and protein content and low in fat content was prescribed and the patient was dismissed.

He returned in December, 1950. Hepatomegaly and splenomegaly were less evident. An excretory urogram revealed that the calculus that had been present in the left kidney had moved into the upper part of the ureter and that it was much larger. There was pronounced hydronephrosis on the left. The serum protein measured 7.6 gm. per 100 cc., with 3.9 gm. of albumin and 3.7 gm. of globulin. The value for blood urea was 78 mg. per 100 cc. The urine contained numerous erythrocytes and leukocytes. The stone was removed surgically from the ureter and recovery was uneventful. The patient's general health has continued to be excellent, with no evidence of recurrent renal calculi or progressive renal insufficiency.

CASE VIII. A twenty-eight year old white man was admitted in August, 1951, complaining of anorexia, nausea, vomiting and inflammation of the eyes. Similar episodes that lasted one to three months had recurred since 1945. In August, 1948, he was placed in a tuberculosis sanatorium because of the finding of bilateral pulmonary infiltrations. When studies failed to confirm a diagnosis of tuberculosis, a tentative diagnosis of sarcoidosis was made. In December, 1948, he was given a therapeutic trial of 20,000 units of vitamin D per day. Within twelve days the concentration of serum calcium became increased and nausea and vomiting developed; hence, administration of the drug was discontinued. There was no history of antecedent renal disease.

On examination, the blood pressure was 140/110. There was congestion of the conjunctival vessels bilaterally. Lymph nodes in the subauricular regions were enlarged. A few small lymph nodes were present in the inguinal regions.

Urinalysis disclosed a specific gravity of 1.010, an acid reaction, albuminuria, grade 2, and the presence of a few leukocytes. The value for hemoglobin was 12.2 gm. per 100 cc. of blood. The sedimentation rate was 42 mm. in one hour. The blood urea measured 62 mg. per 100 cc., the total protein 7.4 gm. with 4.4 gm. of albumin and 3.0 gm. of globulin, the serum calcium 12.1 and 11.5 mg., the serum inorganic phosphorus 3.2 and 3.1 mg., and the alkaline phosphatase 4.4 Bodansky units. Roentgenographic examination revealed disseminated, nodular infiltrations in the upper part of both pulmonary fields. The roentgenographic appearance of the skull, wrists and hands was normal. A duodenal ulcer was demonstrated on a roentgenogram of the upper part of the gastrointestinal tract. Cultures of sputum and gastric washings failed to disclose tubercle bacilli, and the reaction to a tuberculin skin test was negative. On a quantitative diet low in calcium content the patient excreted 151, 126 and 115 mg. of calcium in the urine on three successive days. An excretory urogram revealed no nephrocalcinosis or renal calculi. Examination of the eyes with the slit lamp disclosed early band-shaped dystrophic lesions of each cornea and posterior synechiae in the left eye. Microscopic examination of a lymph node removed from the groin revealed a chronic granuloma without caseation; histologically, the appearance of this lesion was compatible with a diagnosis of sarcoidosis.

The initial clinical impression had been primary hyperparathyroidism. However, the bilateral pulmonary infiltration, the normal values for serum inorganic phosphorus, the absence of hypercalciuria and the biopsy findings characteristic of Boeck's sarcoid made it seem highly unlikely that the patient had hyperparathyroidism. Cervical exploration was not advised. The azotemia was considered to be a secondary manifestation of sarcoidosis. No follow-up studies have been available.

COMMENT

The significant clinical and laboratory findings in the eight cases are summarized in Table I. All the patients were men. Roentgenograms of the thorax revealed pulmonary lesions in six of the eight cases. These lesions included widespread, bilateral, miliary infiltration in four cases and bilateral diffuse fibrosis in two cases. A large mediastinal tumor was found in one case. The hands and wrists in six cases and the skull in four cases presented a normal x-ray appearance.

Hypercalcemia, that is, a value of more than 10.5 mg. per 100 cc. for serum calcium, was present in six cases. Significant hypercalciuria was found in two patients while they were on a diet that contained 135 mg. of calcium per day but was absent in the only other patient studied in this manner. The concentration of serum inorganic phosphorus was abnormal in only one patient (Case II). This patient had significant azotemia with a value of 5.4 mg. for serum inorganic phosphorus.

TABLE 1

SIGNIFICANT LABORATORY, ROENTGENOLOGIC AND TISSUE-BIOPSY FINDINGS IN EIGHT CASES OF SARCOIDOSIS WITH RENAL COMPLICATIONS

Case	Age and Sex	Biopsy Specimen*	Roentgenograms			Blood Levels (mg./100 cc.)			Urinary Excretion of Calcium (mg./24 hr.)
			Thorax	Bones Shown to Be Normal	Kidneys	Urea	Calcium	Phosphorus	
I	30, M	Mediastinal lymph nodes	Large mediastinal tumor	Skull, hands, legs	Calculi in right ureter and right renal pelvis	58 62	12.6 12.2	2.8 3.1	...
II	74, M	Peripheral lymph node	Normal	Skull, hands	Right renal calculus	98 124	11.9 11.6	5.4 4.6	288 259 263
III	31, M	Skin	Diffuse bilateral miliary infiltration	Hands	Right renal and probable left renal calculi	....	9.3	....	...
IV	30, M	Peripheral lymph node	Diffuse bilateral miliary infiltration	Hands, feet	Right nephrocalcinosis	110	13.6	3.9	...
V	72, M	Deep cervical lymph node	Diffuse bilateral fibrosis	Skull	Multiple calculi in left renal pelvis	44	10.9 10.8	3.8 4.2	423 431 327
VI	33, M	Peripheral lymph node	Diffuse bilateral infiltration	Hands	No calculi (later, calcium oxalate stone passed)	98 28†	14.5 13.2†	3.9 3.3†	...
VII	45, M	Liver*	Diffuse bilateral fibrosis	.....	Left renal calculus	60	10.1	3.4	...
VIII	28, M	Peripheral lymph node	Diffuse bilateral miliary infiltration	Skull, hands	No calculi	62	12.1 11.5	3.2 3.1	151 126 115

* Non-caseous granulomas present in all cases except that non-caseous granulomatous hepatitis was present in Case 7.

† Three weeks after administration of vitamins was discontinued.

Albuminuria was present in every case and hematuria was present in five cases. The blood urea was increased in six cases. Roentgenograms of the urinary tract, obtained in every instance, demonstrated renal calculi in five cases and nephrocalcinosis in one. Two of the patients with renal calculi had normal values for serum calcium at the time of study. Conceivably, hypercalcemia and hypercalciuria may have been present during some earlier stage of their illness. Renal insufficiency without roentgenographic evidence of nephrocalcinosis or renal calculi was present in two cases. A history of antecedent renal damage could not be elicited in any instance; neither could the possibility of such damage be definitely excluded.

Tissue biopsy was performed in each of the eight cases; non-caseous granulomatous lesions compatible with a diagnosis of sarcoidosis were found in enlarged peripheral lymph nodes of four patients and in a deep cervical node of another patient. Similar changes were found in the mediastinal nodes removed in Case I. Needle biopsy of the liver (Case VII) revealed granulomatous hepatitis characterized by the presence of non-caseous tubercles, while a skin biopsy (Case III) showed non-caseous granulomas compatible with a diagnosis of sarcoidosis. Tuberculin skin tests made in five cases with first-strength and second-strength purified protein derivative gave a negative response in each case.

Initially, a tentative diagnosis of primary hyperparathyroidism was considered in three cases. However, in only one case was exploration performed for parathyroid tumor suspected of being located in the mediastinum. In this patient, there were no clinical or laboratory findings to suggest sarcoidosis, aside from the unexplained hypercalcemia and renal calculi. Specific findings on biopsy of the lymph nodes in the other two cases led to the correct diagnosis and obviated cervical exploration. In one of these patients a deep pre-scalene node was excised in the absence of peripheral adenopathy.

In the light of recent work by Henneman and co-workers,[7] it is interesting to note the possible role of hypersensitivity to vitamin D as an aggravating factor in the development of hypercalcemia and renal damage in two of our cases. In Case VIII hypercalcemia and gastrointestinal symptoms developed after only twelve days of a daily dose of 20,000 units of vitamin D. The value for serum calcium returned to normal and the gastrointestinal symptoms abated when the use of vitamin D was discontinued. The other patient (Case VI) had severe azotemia, with a value of 14.5 mg. per 100 cc. for serum calcium. He had been taking one multiple-vitamin capsule daily which contained approximately 1,000 units of vitamin D. Three weeks after the use of vitamin D had been discontinued the value for blood urea had returned to normal and the value for serum calcium had decreased to 13.2 mg. Whether this represented an abnormal sensitivity of the patient to vitamin D, with increased absorption of calcium from the gut, or whether it represented a concomitant spontaneous remission of the sarcoidosis remains conjectural.

Death occurred in only one case in this series. Microscopic examination of the kidneys in this case revealed pyelonephritic scars, dystrophic and metastatic calcification, and numerous non-caseating granulomas.

Granulomatous lesions in the kidneys were described by Schaumann[8] in 1933. The clinical finding of hypercalcemia in sarcoidosis was first recognized in 1939.[1] Renal insufficiency in sarcoidosis was initially attributed to massive granulomatous infiltration of the kidneys. In 1948 Albright and Reifenstein[9] pointed out that hypercalcemia in sarcoidosis is associated with hypercalciuria. They suggested that nephrocalcinosis or renal calculi or both may be secondary to hypercalciuria and reported a case of sarcoidosis with bilateral renal calculi as the presenting manifestation. Recent reviews of necropsy cases of sarcoidosis have stressed the relatively infrequent finding of granulomatous infiltration of the kidneys. Branson and Park[10] reported that the kidneys were involved in only eight of 117 cases, while Longcope and Freiman[11] observed renal granulomas in four of thirty cases.

Klatskin and Gordon[4] have also suggested that renal failure in sarcoidosis may be due to hypercalcemia and nephrocalcinosis, although in the two cases they reported roentgenologic evidence of nephrocalcinosis was lacking. Berger and Relman[5] recently reported a case of renal impairment due to sarcoid infiltration of the kidney proved by renal biopsy before and after treatment with cortisone. Hypercalcemia was not present in this case and no microscopic evidence of nephrocalcinosis was found. From these findings, one must conclude that renal insufficiency may develop secondary to either nephrocalcinosis or granulomatous infiltration of the renal parenchyma.

Hypercalcemia *per se*, irrespective of its cause, may lead to severe and irreversible renal damage. Renal impairment is frequently encountered in primary hyperparathyroidism, hypervitaminosis D and milk-alkali syndrome. The common finding in all of these conditions is hypercalcemia, with renal insufficiency, renal calculi and nephrocalcinosis developing as secondary complications. The mechanism by which hypercalcemia *per se* causes renal insufficiency is not fully understood. The renal stones in sarcoidosis, as in primary hyperparathyroidism, are usually composed of calcium oxalate.

The cause of disturbed calcium metabolism in

sarcoidosis remains obscure. Initially, the hypercalcemia was considered to be secondary to the high levels of serum protein seen in sarcoidosis; however, cases of sarcoidosis have also been reported in which there was hypercalcemia without an associated increase in the serum protein.

Active destruction of bone from widespread involvement by sarcoid deposits was then proposed as an explanation of the hypercalcemia. Significant radiologic findings in the skeletal system in sarcoidosis are usually confined to the hands and feet, although generalized rarefaction of bone has been reported. Dent and co-workers[6] concurred in the opinion that the most probable explanation of the hypercalcemia is widespread bone destruction that often is not demonstrable on routine roentgenograms. Davidson and associates[12] recently presented a review of seven cases of nephrocalcinosis associated with sarcoidosis in which hypercalcemia was present in every case. The only roentgenologic evidence of bone involvement by sarcoid lesions was found in one case in which there was a single site of cystic destruction in the end of one phalanx.

The possibility of parathyroid overactivity associated with sarcoidosis has been postulated. Parathyroid hyperplasia has been reportedly found in a few cases of sarcoidosis with hypercalcemia,[11] but most observers[4,9] have reported that the parathyroid glands are normal.

Henneman and associates[7] have recently proposed a theory of excessive endogenous production of vitamin D-like substances with increased absorption of calcium from the gastrointestinal tract and possible mobilization from bone. Their balance studies revealed increased gastrointestinal absorption of calcium in three patients with sarcoidosis and hypercalcemia. Administration of cortisone to these patients produced an increase in fecal excretion of calcium and a concomitant decrease in serum calcium.

Hypercalcemia in sarcoidosis may mislead the clinician into making an erroneous diagnosis of primary hyperparathyroidism if other clinical and laboratory evidence for sarcoidosis is lacking. Primary hyperparathyroidism without bone disease but with renal failure may manifest itself in an identical clinical pattern, since the concentration of serum inorganic phosphorus (usually reduced in primary hyperparathyroidism) may become normal or increased when renal function becomes impaired in this condition. The differential diagnosis under these conditions may be most difficult. Negative results on exploration of the neck for a parathyroid tumor have been reported in several cases[4,9] in which sarcoidosis later proved to be present.

Determination of the serum calcium is important in every case of suspected sarcoidosis, since irreversible renal complications may develop if no effort is made to lower an abnormally high level of serum calcium. In some cases a high intake of fluid and a diet low in calcium content may lead to improvement in renal function coincident with decrease in serum calcium. Recent reports[13,14] describing the effectiveness of cortisone and corticotropin (ACTH) in the treatment of sarcoidosis are encouraging. In the case of Dent and associates,[6] cortisone produced a pronounced reduction in the serum calcium and serum globulin, with subsequent improvement in renal function. As noted, in the studies reported by Henneman and associates cortisone lowered the concentration of serum calcium and increased the fecal excretion of calcium in three cases of sarcoidosis with hypercalcemia. The mechanisms by which cortisone or ACTH produce these findings remain to be elucidated. Obviously, the degree of recovery in renal function will be dependent upon the extent of irreversible glomerular and tubular damage associated with the deposition of calcium salts and with granulomatous infiltration. Early recognition and treatment are important in cases of sarcoidosis with hypercalcemia if these renal complications are to be prevented.

SUMMARY

In eight cases of sarcoidosis in which renal complications were present, renal calculi were demonstrable in five cases, nephrocalcinosis in one case and renal insufficiency in two cases. Hypercalcemia was present in six of the cases.

The possible mechanisms for the hypercalcemia are discussed.

Renal insufficiency may be secondary to widespread granulomatous infiltration, nephrocalcinosis, or a combination of both processes.

REFERENCES

1. Harrell, G. T. and Fisher, S. Blood chemical changes in Boeck's sarcoid with particular reference to protein, calcium, and phosphatase values. *J. Clin. Investigation*, 18: 687, 1939.

2. Rotenberg, L. and Guggenheim, A. Boeck's sarcoid (report of case with renal involvement). *Dis. Chest.*, 8: 392, 1942.
3. Klinefelter, H. F., Jr., and Salley, S. M. Sarcoidosis simulating glomerulonephritis. *Bull. Johns Hopkins Hosp.*, 79: 333, 1946.
4. Klatskin, G. and Gordon, M. Renal complications of sarcoidosis and their relationship to hypercalcemia: with a report of two cases simulating hyperparathyroidism. *Am. J. Med.*, 15: 484, 1953.
5. Berger, K. W. and Relman, A. S. Renal impairment due to sarcoid infiltration of the kidney: report of a case proved by renal biopsies before and after treatment with cortisone. *New England J. Med.*, 252: 44, 1955.
6. Dent, C. E., Flynn, F. V. and Nabarro, J. D. N. Hypercalcemia and impairment of renal function in generalized sarcoidosis. *Brit. M. J.*, 2: 808, 1953.
7. Henneman, P. H., Carroll, E. L. and Dempsey, E. F. The mechanism responsible for hypercalcuria in sarcoid. *J. Clin. Investigation*, 33: 941, 1954.
8. Schaumann, J. Étude anatomo-pathologique et histologique sur les localisations viscérales de la lymphogranulomatose bénigne. *Bull. Soc. franç. dermat et syph.*, 40: 1167, 1933.
9. Albright, F. and Reifenstein, E. C. The Parathyroid Glands and Metabolic Bone Disease: Selected Studies. Baltimore, 1948. The Williams & Wilkins Company.
10. Branson, J. H. and Park, J. H. Sarcoidosis—hepatic involvement: presentation of a case with fatal liver involvement, including autopsy findings and review of the evidence for sarcoid involvement of the liver as found in the literature. *Ann. Int. Med.*, 40: 111, 1954.
11. Longcope, W. T. and Freiman, D. G. A study of sarcoidosis based on combined investigation of 160 cases including 30 autopsies from The Johns Hopkins Hospital and Massachusetts General Hospital. *Medicine*, 31: 1, 1952.
12. Davidson, C. N., Dennis, J. M., McNinch, E. R., Willson, J. K. V. and Brown, W. H. Nephrocalcinosis associated with sarcoidosis: a presentation and discussion of seven cases. *Radiology*, 62: 203, 1954.
13. Shulman, L. E., Schoenrich, E. H. and Harvey, A. McG. The effects of adrenocorticotrophic hormone (ACTH) and cortisone on sarcoidosis. *Bull. Johns Hopkins Hosp.*, 91: 371, 1952.
14. Siltzbach, L. E. Effects of cortisone in sarcoidosis: a study of thirteen patients. *Am. J. Med.*, 12: 139, 1952.

Review

A Survey of Allergy's Present Position*

Classification of Clinical and Pathologic Features of Allergic Disorders

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ALLERGY is a unique specialty. It is not assigned to a given organ, system of organs, sex or age; neither are its members users of the Roentgen ray or scalpel. Much of the work rightfully belonging to allergists therefore has been performed by specialists in other fields interested only in the specific problem falling within their domain. This situation often has not worked out well for the patient, who needs understanding of his allergic constitution rather than mere symptomatic treatment of the local or presenting problem. It is consequently in the general interest to point out the main relationships, mechanisms and complexities of allergic disorders. The proper domain of the allergist and the necessity of his special training can then be recognized.

In which disorders should the allergist be the managing physician? In which should he be an associated physician? In which would he be a desirable consultant? To facilitate answering these questions, from a clinical and statistical viewpoint, the allergic disorders will be divided into three categories. In Group I are included those diseases invariably or usually due to allergy, hypersensitivity, altered reactivity or disordered immunology—whichever definition one prefers. In Group II are those disorders in which allergy is frequently the cause, determined either from the history or by objective demonstration. Group III includes these disorders which are uncommonly allergic in origin, occur with suggestive frequency in association with or following recognized allergic disorders and have similarities to recognized allergic disorders in respect to the clinical course or findings, or in which apparently unrelated abnormal immunologic phenomena can be demonstrated.

The pathologist can help in our inventory, both of inclusion and subdivision. A useful pathologic classification has to be based upon the predominant type of tissue reaction.[15] A division into anaphylactoid, necrotizing, granulomatous and hyalinoid classes becomes apparent. Logical subgroups are cell selective and tissue selective groups in the necrotizing class, tuberculoid and rheumatoid in the granulomatous class, and collagen diseases and amyloidosis in the hyalinoid class. However, we are faced with the fact that, although characteristic pathologic changes occur in allergic disorders, they are rarely pathognomonic. For practically every allergic mechanism there may be a non-allergic mechanism which produces similar histologic changes. In animal experimentation the changes produced by allergic mechanisms in one species may be produced by non-allergic mechanisms in others. Another difficulty stems from disorders which elicit more than one type of tissue reaction, or which gradually or suddenly change from one to another. Periarteritis nodosa, for example, can show any combination of anaphylactoid, hyalinoid or necrotizing lesions, or can show any given one at a time.[65] However, similarities are more important than differences for our purposes.

In Tables I to IV the allergic disorders are enumerated and a tentative classification that embraces the concepts of both clinician and pathologist is offered. Alternative classifications are in parentheses. Reference numbers are indicated in the tables wherever rarity, necessity for evidence or recent information is required. Drug reactions are purposely excluded, for over 500 drugs have been proved to be sensitizing

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TABLE I

ALLERGIC DISORDERS WITH ANAPHYLACTOID TISSUE REACTIONS

Group I	Group II	Group III
Allergic rhinitis, seasonal and perennial	Migraine[4,22]	Erythema multiforme[7]
Bronchial asthma	Epilepsy[22]	Retinal detachment[111]
Atopic eczema[83]	Ménière's disease[3,4]	Retinal edema and hemorrhage[111]
Contact dermatitis[34,83]	Intermittent hydrarthrosis	Uveitis[24,111]
Dermatophytids[34,83]	Conjunctivitis[24,111]	Reiter's disease[70,72]
Urticaria and angioneurotic edema	Episcleritis[24,111]	Loeffler's syndrome[5]
Anaphylactic shock	Scleritis[24,111]	Temporal arteritis[29,47]
Rheumatic pneumonia[86]	Keratitis[24,111]	Ulcerative colitis[2]
Pneumonia caseosa[87]	Erythema nodosum[119]	Regional enteritis[13,107]
Gastrointestinal allergy[2]	(Periarteritis nodosa)[65,118]	
Lermoyez's syndrome[27]	Glomerulonephritis[28,64,68]	
Mild serum sickness	Canker sores[8]	
	Exacerbations of gout[50,53]	
	Sudden death in the hyperreactor state[114]	

TABLE II

ALLERGIC DISORDERS WITH NECROTIZING TISSUE REACTIONS

Group I	Group II	Group III
	Cell Selective	
Rh sensitization[117]	Granulocytopenia	Favism[78]
Transfusion hemolysis[76]	Thrombocytopenic purpura[54,77,113]	"Toxic" aspermia[56]
	Aplastic anemia	
	Hemolytic anemia[120]	
	Tissue Selective	
"Carbuncle" of kidney[14]	Acute pancreatic necrosis[48,110]	Encephalomyelitis[60,81]
Diffuse necrosis of renal cortex[112]	Acute yellow atrophy of liver	Demyelinizing diseases[37]
Acute dermal necrosis	Acute bone marrow necrosis	Multiple sclerosis[16,39]
	Necrotizing appendicitis[25]	Acute parotid necrosis
	Necrotizing cholecystitis[106]	(Ulcerative colitis)[2]
	(Periarteritis nodosa)[65]	

agents and an example could be found in any class.[17,19]

ALLERGIC DISORDERS WITH ANAPHYLACTOID TISSUE REACTIONS

Anaphylactoid tissue reactions are exudative and are either serous, fibrinous, hemorrhagic or purulent. Edema may sometimes be the sole feature; fixation methods may not preserve it properly. Smooth muscle spasm is a functional reaction not apt to be demonstrable histologically.

ALLERGIC DISORDERS WITH NECROTIZING TISSUE REACTIONS

Necrotizing lesions may be limited to a specific type of cell (usually one of the blood elements) or to a specific tissue. The lesions resemble those produced experimentally by the Arthus and Shwartzman methods. The concentration of the

TABLE III

ALLERGIC DISORDERS WITH GRANULOMATOUS TISSUE REACTIONS

Group I	Group II	Group III
	Tuberculoid	
Tuberculosis[87] Coccidioidomycosis Sporotrichosis Tularemia Brucellosis Beryllium granuloma[51]	Sarcoidosis[62,98,108]	Histoplasmosis
	Rheumatoid	
Rheumatic fever[9,85,88] Sympathetic ophthalmia[24,80]	Rheumatoid arthritis[9,88,100] Giant cell rheumatoid granuloma of nose[73,115] Rheumatoid scleritis[24,101] A. Brawny scleritis B. Scleromalacia perforans	Eosinophilic granuloma of bone[102] (Loeffler's syndrome)[5]

TABLE IV

ALLERGIC DISORDERS WITH HYALINOID TISSUE REACTIONS

Group I	Group II	Group III
	"Collagen Diseases"	
Schönlein-Henoch syndrome[40,77,113] Severe serum sickness[88] Atopic cataract[24,97,111]	Periarteritis nodosa[65,88,118] Disseminated lupus erythematosus[88,109] Libman-Sacks syndrome[49] Thromboangiitis obliterans[52] (Glomerulonephritis)[95,103]	Dermatomyositis[61] Scleroderma[61] Sclerema neonatorum[61]
	Amyloidosis	
Amyloidosis of chronic tuberculosis and staphylococcus infection[58]	Amyloidosis in association with hyperglobulinemia[23,58,105]	?

antigen-antibody reaction complex and the (induced) susceptibility of the tissue determine the site of the lesion.

ALLERGIC DISORDERS WITH GRANULOMATOUS TISSUE REACTIONS

The essential architecture of granulomas of allergic origin comprises a central area of necrosis surrounded by proliferated reticuloendothelial cells which often assume a radial, palisaded arrangement. Giant cells of the foreign body or Langhans type may or may not be present. In the tuberculoid type the central area of necrosis is caseous and is in the proliferated inflammatory tissue. In the rheumatoid type the necrosis is fibrinoid and is in pre-existing collagen. Necrosis is absent, however, in sarcoidosis, which otherwise fits into the tuberculoid group, and in sympathetic ophthalmia, which otherwise belongs with the rheumatoid group.

ALLERGIC DISORDERS WITH HYALINOID TISSUE REACTIONS

The specific antigen-antibody reaction may result in the formation of extravascular precipitates, usually in the reticuloendothelial system where the concentration of antibody is highest. There are, therefore, many forms of hyalin, of which amyloid has been the most easily characterized by staining reactions; even the amyloids vary, however, particularly in their reaction to iodine.[58] Persistent and repeated stimulation of the immune mechanisms, usually by chronic or recurrent infection, and association with hyperglobulinemia[23] and plasmacytosis are fundamental factors in the production of amyloidosis.[58] With collagen disorders, hyalinoid reactions other than amyloidosis, the factor of infection is conspicuously absent except in the case of poststreptococcal glomerulonephritis, and the nature of the stimulation is often unclear. Ehrich considers the collagen disorders to be dysgammaglobulinemia.[33] However, antibodies are found in both the beta and gamma globulin fractions in man. Allergy as a cause of hyperglobulinemia is well recognized.

ANTIGENS, LOCALIZATION OF LESIONS AND THEORIES OF ALLERGIC REACTIONS

Two reasons why it may be difficult to accept new additions to the realm of allergy are the frequent undemonstrability of the antigens involved and the inability to account for localization of lesions in any given disease. Extrinsic allergy, such as to pollen, animal dander or food, is unquestionably accepted. It is still not possible, however, to account for the production of asthma in one person, rhinitis in another, urticaria in a third, purpura in a fourth, and so on, by the same antigen; nor is it possible to explain why the same antigen should produce different symptom-complexes in the same person at different times. Antigens may be formed intrinsically through microbial infection,[75] through alteration of the body proteins by physical and chemical means,[69] or through haptene linkage of drugs or other relatively simple chemicals with the body proteins.[41,69,75] Not only the haptene but the linked protein may confer specificity.[34] Why, then, can we not accept the idea that characteristic localizations can occur in the less common disorders[61] or from autoantigens? In periarteritis nodosa the vascular system, lungs and kidneys are primarily affected. In disseminated lupus erythematosus the skin, kidney and heart valves are most commonly involved, whereas in dermatomyositis the skin, oral cavity and muscles, and in scleroderma the skin and joints are affected primarily. In rheumatic fever the joints and heart suffer the major damage, less often the lungs, brain and skin. In rheumatoid arthritis the joints and muscles suffer primarily, but at times the skin and heart are involved.

The classical concept of antibodies formed from a primary sensitization becoming anchored to tissue cells and later reacting with subsequently introduced antigen requires modernization. We know that in serum sickness and penicillin sensitivity in which the antigen is introduced only once, part of the inciting agent becomes anchored directly to tissue cells and the remainder that is not metabolized or excreted stimulates the antibody-producing mechanisms. The recurrent waves of clinical exacerbations coincide with successive releases of antibody, which combines with fixed antigen. Localization of the allergic manifestations following streptococcal infection is more easily understood if we realize that the *antigen* becomes sessile first in cardiovascular and renal structures. It must also be realized that capillaries inflamed from any cause are more permeable to protein, hence either antigen or its specific antibody tends to accumulate in inflamed structures. The clinical form assumed by an allergic response may even be determined by the manner in which an antigen is reapplied or reintroduced. For example, the superficial application of tuberculin to the skin, as in the patch test, results in the lesion of contact dermatitis, whereas tuberculin injected intradermally, as in the Mantoux test, produces the classical delayed "tuberculin type" response.

The simple and useful "histamine theory" is, unfortunately, too simple. Reproduction of many of the reversible and rapidly produced symptom-complexes in the anaphylactoid class by histamine is indeed possible but histamine has no presently discernible role in the other forms of allergic disease.[55] Allergic subjects are more susceptible to the pharmacologic effects of histamine and less able to inactivate it, being in these respects similar to adrenalectomized animals.[6,21,92] However, no correlation exists between blood histamine levels and the production of symptoms.[93] Histamine is now known to be widely distributed throughout the body tis-

TABLE V

CORRELATION OF CLINICAL OBSERVATIONS WITH TYPE OF TISSUE REACTION

Histologic Class	Type of Necrosis	Skin Reaction	Serum Antibody (passive transfer)	Increased Serum Globulin	Specific Infection	Eosinophilia	Tissue Plasmacytosis	Response to Antihistamines	Response to ACTH and Cortisones
Anaphylactoid	* (fibrinoid)	immediate wheal type	often *	usually 0	0 or *	0 to ****	0 or *	0 to ****	0 to ****
Necrotizing	**** (diffuse)	0 or necrosis	0 or *	0	0 or *	0 or *	* or **	0	Cell selective * to *** Tissue selective adverse to *
Granulomatous: Tuberculoid	** (caseous)	delayed "tuberculin type"	0	0 to ***	*	0	*	0	Microbial tuberculoid adverse; non-microbial tuberculoid **
Rheumatoid	** (fibrinoid)	0	0	0 to **	0	0 or *	*	0	** to ****
Hyalinoid: Collagen diseases	** (fibrinoid)	0	0	* to ***	0	0 or *	* to ****	0	0 to ****
Amyloidosis	0	0	0	* to ****	0	0	** to ****	0	usually 0

Note: 0 = absence; * to **** = presence in increasing degree.

sues, virtually all of it being held within the cells in loose combination. The amounts normally present vary tremendously. Histamine exerts its effects only when it is released from the cells and passes to the extracellular spaces. The only known mechanism for destroying histamine is histaminase, although in human subjects it is presently demonstrable only in the plasma of pregnant women.[1] Were histamine the sole activator of allergic phenomena our "antihistaminic" drugs or blocking agents would be more effective; actually they often can not relieve or prevent symptoms that histamine can initiate, for example, asthma. The concept of the antigen-antibody union on the cell surface activating a proteolytic enzyme system[90] (plasmin) resulting in the liberation of histamine and heparin[59] does not embrace all known allergic phenomena. The suggestion of Rocha e Silva[91] that the humoral "anaphylatoxin theory" be revived in the light of newer knowledge merits serious consideration. Its unification with the cellular "histamine theory" is now possible since it is shown that anaphylatoxin may also exert its effects through a histamine mechanism. Just why citration prevents activation of anaphylatoxin and release of histamine from cells, and why certain mucopolysaccharides activate the anaphylatoxin precursor is still unsettled.[91] Godlowski's enzymatic concept of allergy is also worthy of study.[44]

Now let us see how the clinical and immunologic observations fit in with the histologic classification.

ANTIBODIES IN SKIN AND SERUM

Skin reactions fall into a logical type pattern: wheals for the anaphylactoid, delayed "tuberculin type" for the tuberculoid, necrotic for the necrotizing and negative for the others. The antibody is more apt to be carried by the plasma in the case of wheal reactions and to be present in the cells in the case of "tuberculin type" and necrotizing reactions.[42] The demonstration of specific antibodies in the serum by the methods of classical immunology is usually accomplished in the anaphylactoid class, frequently in the necrotizing, and rarely in the granulomatous or hyalinoid classes. Gross increases in the serum globulin fractions are more apt to be noted in the latter two classes, however.

More than one type of antibody can be produced by stimulation with a single antigen.[79] The so-called "complete" precipitating and agglutinating antibodies with high affinity for antigen are well known. "Incomplete" antibodies include: reagins, with high affinity for tissue cells and usually high affinity for antigen; inhibiting or blocking antibodies, with high affinity for antigen and low affinity for tissue cells; coprecipitating antibodies, with intermediate affinity for antigen; and incomplete

antibodies, with a low affinity for antigen detected only by special technics such as that of Coombs. The antibodies formed vary with the timing, nature of the antigen, route of administration, and even with the subject.[79] Better correlation of fractionation and chromatographic and electrophoretic studies with the results of skin tests, precipitin reactions, agglutination tests, complement fixations, and the like can reasonably be expected.

SPECIFIC INFECTION AND ALLERGY

Specific infection can be demonstrated in the tuberculoid granulomas of microbial origin and can frequently be demonstrated in the tissue selective necrotizing class. The association of glomerulonephritis[28] and rheumatic fever[82] with hemolytic streptococcus infection is well recognized, and rheumatoid arthritis may be similarly related.[100] The presence of specific bacteria is not usually or consistently demonstrable in these conditions, however. Microbial infection in the anaphylactoid class is usually only a trigger factor, but is specific with dermatophytids and erythema nodosum.

THE ROLE OF SPECIFIC CELLS IN ALLERGIC PHENOMENA

Eosinophilia is an interesting confirmatory observation in the diagnosis of allergic disorders but it is certainly not pathognomonic, nor is it invariably present.[10] When present, eosinophilia may roughly parallel the clinical severity of the disease. It is not known why the shock tissues have a special affinity for eosinophils,[10] unless they are the transporters of antigen to these sites or the antigen present there transforms other types of cells in these tissues into eosinophils.[44] Eosinophils in exudates, pus or biopsy specimens are frequently overlooked because of incorrect staining and lack of suspicion of this possibility. Godlowski[44] conceives of eosinophils as evolving from "inadequate" cells of diverse origins. The enzyme systems of such cells lack the immediate capacity to destroy foreign protein, and the latter acts as a stimulus for the reorganization of the intracellular proteolytic enzymes. The new proteinase of this adaptation not only can catabolize the foreign protein molecules, but in the anabolic phase can reconstitute the antigenic protein within the cell, incorporating it within its own structure. The simultaneously acquired property of amoeboid motion facilitates the spread of these antigen bearing cells throughout the organism. Possession of this toxic protease remains a permanent and transmissible feature of these cells.[44] It is known that the eosinophils in the tissues are unaffected by cortisone and hydrocortisone[44] (directly or through anterior pituitary corticotropin) and that these compounds have no direct effect upon antigen. The diminution of circulating eosinophils by these compounds, with concomitant improvement in many allergic manifestations, suggests a protective mechanism at the precell level. The first consequence of hormonal action is degranulation, and disintegration follows. Eosinophils also may be stored temporarily in some internal organ such as the spleen, and/or their release or production in the bone marrow inhibited.[10] Ascorbic acid and heparin block the eosinopenic effects of these 17-hydroxycorticosteroids. No correlation exists between blood eosinophil and blood histamine levels after administration of ACTH and cortisone.[93] By way of further complicating the situation, histamine injection alone can cause transient eosinopenia independently of adrenocortical activity by causing temporary storage of these cells in tissues;[133] stimulation of the bone marrow may cause subsequent esosinophilia. Epinephrine may also cause eosinopenia by its peripheral action.

The polymorphonuclear neutrophilic leukocytes have some interesting associations with allergy. They, too, are lysed in the circulation when cortisone is administered but, since in disintegration they release a leukocyte-promoting factor, this mobilization from the bone marrow masks the lytic process or may even overcompensate for it.[44] They enter into the formation of lupus erythematosus cells, a reasonably specific sign of disseminated lupus erythematosus[57] but one strangely absent in apparently closely related disorders. Their presence is necessary for production of Arthus and Shwartzman reactions, the latter being inhibited by agents causing leukopenia.[104,112] It is well known that addition of the specific antigen to the leukocytes of a sensitized subject results in their impaired function[20] or in death[84] and histamine release.[63] Thrombocytes may also be diminished in allergic reactions.[54,77,105,113]

Lymphocytes are now thought to occupy a minor role, if any, as producers of antibody. Their disintegration and diminution in lymphoid tissue as a result of ACTH, cortisone and hydrocortisone administration for the relief of allergic disorders seems more an incidental than a

necessary phenomenon. Such antibody as is present in the cytoplasm of the lymphocyte is not necessarily formed there.

Monocytes, macrocytes and reticuloendothelial cells, formerly thought to be the antibody producers, merely degrade corpuscular material to antigenically active molecules.[71,96] The latter are then released at varying rates to plasma cells, the main and perhaps sole producers of antibodies.[11] Bacteria and dissolved antigen are agglutinated or precipitated on the surface of plasma cells, from which antibody can later be extracted. As far as presently available biopsy and autopsy material indicate, plasmacytosis seems to be the common denominator in allergic disorders.[35,89] The plasma cell, no matter what its source, is the morphologic sign of antibody production. Immature plasma cells accumulate in lymphadenoid structures[12] and the spleen[12,35] during the early stages of immunization or sensitization and multiply, as shown by formation of chromosomal desoxyribose nucleic acid.[32] Later, when antibody production is at its peak, mature plasma cells become conspicuous.[12,35] Ehrich has shown that antibody production parallels the production of cytoplasmic protein and ribose nucleic acid.[32] Examination of plasma cells by Caspersson's microspectrographic technic shows that protein synthesis proceeds very rapidly in the cytoplasm. Plasma cells frequently contain Russell bodies, which are believed to represent retained protein secretions.[33] Fagraeus[36] believes that reticuloendothelial cells produce antibodies and develop the morphologic characteristics of plasma cells. The cell responsible for antibody production, in any case, must be long lived and capable of retaining permanently the stimulus of a brief exposure to an antigen, or must be able to pass on this capacity to its descendants.[116]

The monocytes contain lipase in addition to the nucleinase, proteinase and carbohydrase found in the neutrophils. This enables them to break down more varieties of particulate matter (including lipoid coated bacteria) to soluble antigenic material.[121] Injection of adrenal cortical extract results in monocytopenia followed by monocytosis.[122] With respect to the enzyme systems of the basophilic polymorphonuclear leukocytes, little is known.

A functional and probably anatomic relationship exists between basophils and mast cells.[123,124,125] Administration of cortisone reduces the number of basophils in the circulation[123] and mast cells in the tissues.[123,124] Heparin in tissues is proportional to their mast cell content,[125,126] and the same correlation exists between tissue mast cell and histamine content.[127] Fawcett, using 4$^{8}/_{80}$ histamine liberator, showed the correlation between tissue mast cells and its content of heparin and histamine.[129]

The blood histamine level is proportional to its basophil content, as shown by studies of normal patients and those with granulocytic leukemia and polycythemia vera.[130] Normally these relatively scarce cells carry over one half of the blood histamine, the eosinophils carry one third (in the process of destruction?), and all of the other blood elements combined contain the remaining sixth.[131] Heparin and histamine in the basophilic granules are part of a more elaborate structure including phospholipid and protein.[128] This structure may be disrupted by diverse means, and the activities of the liberated histamine and heparin are independent. They show no tendency to recombine or antagonize each other in the blood stream.[128]

The function of basophils and mast cells in inflammations and allergic reactions would seem to be the delivery of anticoagulant to facilitate absorption or to prevent obstructive clotting of blood and lymph. Their function with respect to histamine is not clear. Histamine liberated as a result of injury may play a part in the mobilization of the fixed tissue cells which precedes repair.[128] Certainly the freedom of patients with leukemia from the common allergic disorders in spite of the relatively enormous amounts of circulating histamine speaks against histamine as the sole effector of allergic manifestations. One may speculate that the local liberation of histamine is what attracts eosinophils to the shock tissues, for the gel-like bodies of the eosinophilic granules contain basic arginine rich proteins which have antihistaminic properties. Detoxification of histamine by eosinophils may also be accomplished by oxidative enzymatic breakdown.[132]

NECROSIS IN ALLERGIC DISORDERS

Caseous necrosis is encountered only in the tuberculoid subclass. Fibrinoid necrosis is a common feature of the subclasses of rheumatoid and collagen disease; it is usually slight or absent in the commonest disorders in the anaphylactoid class. Necrosis is not conspicuous in amyloidosis. Death of tissues and cells is diffuse in the necrotizing class.

RESPONSES TO ANTIHISTAMINES, ACTH, CORTISONE AND HYDROCORTISONE

Clinical response to antihistaminic drugs is limited to the anaphylactoid class of disorders and is quite variable.[55] Asthma may occasionally even be adversely affected.[19] Of practical interest is that these drugs modify or abolish the immediate wheal tests but do not affect the other types of tests. The 17-hydroxycorticosteroids have no effect upon the immediate wheal tests, although they may relieve clinical manifestations, but they prevent development of the delayed "tuberculin type" tests, which are inflammatory in nature.[74,93]

The use of cortisone, hydrocortisone and ACTH in all manner of allergic (and other) disorders is widespread and often irrational.[99] Prednisone and prednisolone are said to produce less retention of sodium and water but clinical reports on long term effects in allergic disorders are not yet available and caution in their use is still indicated.

That the reasons for a classification based on different types and degrees of response to such symptomatic therapy would be impractical is apparent from the following considerations: The corticoids have no destructive effect on antibodies themselves and do not affect the combination of antigen and antibody. They do inhibit antibody synthesis, although not completely,[12,38,43] and they do inhibit inflammatory reactions markedly, but again not completely in doses which can be tolerated for long. The entire inflammatory response may be limited to the appearance of a few macrophages. The danger that microbial infection may become rampant under such therapy is always present and not always preventable or neutralizable by antibiotics.[31] The antihyaluronidase action of the corticoids only partially compensates for suppression of the protective inflammatory reaction. Anaphylactic shock, which may be produced by only traces of antibody, can not, therefore, be suppressed or prevented.[26,38,43] Experimentally, pre- or co-treatment with these corticoids or corticotropin does not inhibit the Arthus or Shwartzman reactions;[38] actually, the protective mechanisms of the animal are eliminated so that the preliminary preparatory dose alone (without the subsequent provocative dose) produces the reaction.[112]

Microbial infection not easily controlled is a contraindication to the use of the corticoids and ACTH, absolute in the case of infectious tuberculoid granulomas and relative in the tissue selective necrotizing subclass, amyloidosis due to infection, and occasional diseases in the anaphylactoid class.[31] The non-infectious tuberculoid granulomas, rheumatoid granulomas, collagen diseases and most members of the anaphylactoid class are benefited. In established amyloidosis they are of no aid. In the necrotizing cell selective subclass of disorders, conditions exhibiting positive evidence of abnormal immunologic processes are helped by the cortisones and ACTH. These conditions include "autoimmunization" hemolytic anemia[120] which gives a positive reaction to the Coombs test, Rh sensitization, transfusion reactions, and idiopathic thrombocytopenic purpura which gives a positive reaction to the Tullis test.[113] In other conditions in this group the effects are variable and unpredictable.

THE QUESTION OF ADRENOCORTICAL AND ANTERIOR PITUITARY DEFICIENCIES

The similarity of the reactions of allergic subjects to adrenalectomized animals[21,93] brings up the possibility of a basic adrenocorticoid or anterior pituitary deficiency in such subjects. Generally speaking, this is not true for the level of production of both kinds of hormones is within normal limits. The doses required for therapeutic effects are above the physiologic range, as evidenced by the development of manifestations of Cushing's syndrome with prolonged use.[99] Rose, Fyles and Venning feel that certain asthmatics are exceptions.[94] They show that the "extrinsic" type had normal corticoid excretion and normal response to ACTH, whereas those of the "intrinsic" type had a lowered output of corticoids, and that ACTH could stimulate normal corticoid production but never above normal. It would appear that the asthmatic state (which certainly seems to be "stressful" enough) is an insufficient stimulus for the anterior pituitary gland, or that some block in the hypothalamic pathway leading to the pituitary is characteristic of this condition.[66,94] Ordinarily, ACTH production and release are reciprocally regulated by the amounts of circulating compounds E and F. It is known that insulin and epinephrine stimulate the hypothalamus directly and that histamine stimulates release of ACTH from the pituitary.[93] Activation of the anterior pituitary gland by the hypothalamus is believed to be accomplished

through a humoral pathway, mediated by a highly antigenic polypeptide. These "intrinsic" asthmatic subjects are not hypoglycemic and the blood histamine fluctuations bear no consistent relationship to the symptoms. They may or may not be "epinephrine-fast." Their blood corticoid levels are not high enough to be depressant. One of two interesting possibilities remaining is that this polypeptide may act as an autoantigen in these persons, producing an inactivating antibody or antihormone. The other is the possibility of ACTH doing the same.[46]

THE ROLE OF HEPARIN

No theory of allergic mechanisms to date completely explains the role of heparin. The known liberation of heparin or heparin-like substances in anaphylactic shock[59] at first glance seems at variance with its property of inhibiting the experimental Arthus and Shwartzman phenomena (local and generalized).[45] However, the minor evil of the transient tendency to hemorrhage could well be a protective mechanism against even greater and irreversible damage from thrombus formation. Heparin, derived from mast cells, is an ingredient of another important protective substance, hyaluronidase inhibitor.[33] Here it is present as an unstable combination with a lipid and a polypeptide; like cortisone, it increases the viscosity and diminishes the permeability of the intracellular ground substance.[33] It is claimed that this complex inhibits antigen-antibody reactions.

THE ALLERGIST'S SPHERE, PRESENT AND FUTURE

By now it should be evident that integrated training and experience in general medicine, immunology, bacteriology, aerobiology, biochemistry, pharmacology and endocrinology is necessary for proper diagnosis and treatment of allergic disorders. Phylactic and prophylactic specific antimicrobial therapy should be practiced when feasible.[67] All too often, however, the sulfonamides and antibiotics are themselves responsible for allergic reactions, some serious.[18] Constant vigilance is necessary, for the antibiotic that was originally the bacterium's nemesis may end as its nutrient.[18] Antihistamines, the corticoids, ACTH and other drugs are welcome aids but nevertheless temporary alleviants of effects, not causes. Migration for relief from allergies is only rarely justified and infrequently successful.[30]

Elimination of the cause is still the desideratum in allergy. If that is impossible, hyposensitization, when feasible, is indicated. The best and most permanent protection, in general, is conferred by blocking antibody or an excess of circulating reagin. No evidence exists that hyposensitization as clinically practiced induces the onset of collagen diseases, rheumatoid disorders, amyloidosis or necrotizing lesions. Arthus reactions to therapeutic doses by allergists have been exceedingly rare in spite of numerous injections of allergens into the same sites. The reported cases include multiple injections of antitoxins, liver extract, insulin, and rabbit brain and spinal cord suspensions for rabies prophylaxis; it would hardly seem that allergists were implicated.

A field rich in potential rewards lies in the investigation of allergenically induced disorders without presently demonstrable skin tests or antibodies. The isolation of autoantigens, the existence of which we now only infer or suspect, possibly could open new groups of diseases to specific therapy. Ways might be found for using the autoantigen to incite formation of protective blocking antibodies. It is conceivable that the specific autoantigen, or even the non-antigenic haptene, might be used to neutralize the autoantibody before it reaches the shock organ.

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Ackroyd, J. F. Allergic purpura, including purpura due to foods, drugs and infections. *Am. J. Med.*, 14: 605, 1953.

Carr E. Drug allergy. *Pharmacol. Rev.*, 6: 365, 1954.

Dameshek, W. Hemolytic anemia. Direct and indirect indications, pathogenetic mechanisms and classifications. *Am. J. Med.*, 18: 315, 1955.

Dresner, E. Aetiology and pathogenesis of rheumatoid arthritis. *Am. J. Med.*, 18: 74, 1955.

Evans, R. S., Takahashi, K., Duane, R. T., Payne, R. and Chi-Kong, Liu. Primary thrombocytopenic purpura and acquired hemolytic anemia. Evidence for a common etiology. *Arch. Int. Med.*, 87: 48, 1951.

Harvey, A. M., Shulman, L. E., Tumulty, P. A., Conley, C. L. and Schoenrich, E. H. Systemic lupus erythematosus: review of the literature and clinical analysis of 138 cases. *Medicine*, 33: 291, 1954.

Klemperer, P. Pathology of systemic lupus erythematosus. Progress in fundamental medicine. Edited by McManus, J. F. A. Philadelphia, 1952. Lea & Febiger.

REFERENCES

1. Ahlmark, A. Studies on the histaminolytic power of plasma, with special reference to pregnancy. *Acta physiol. Scandinav.*, supp. 9: 5–107, 1944.

2. Andresen, A. F. R. Allergy of the gastro-intestinal tract. *Rev. Gastroenterol.*, 18: 779, 1951.
3. Atkinson, M. Observations on the etiology and treatment of Ménière's syndrome. *J. A. M. A.*, 116: 1753, 1941.
4. Atkinson, M. Ménière's syndrome and migraine. Observations on a common causal relationship. *Ann. Int. Med.*, 18: 797, 1943.
5. Baggenstoss, A. H. and Lindberg, D. O. N. Loeffler's syndrome. *Proc. Staff. Meet., Mayo Clin.*, 21: 457, 1946.
6. Banting, F. G. and Gairns, S. Suprarenal insufficiency. *Am. J. Physiol.*, 77: 100, 1926.
7. Barber, H. W. and Forman, L. The results of intradermal tests in certain dermatoses and the therapeutic effect of intradermal vaccines. *Brit. J. Dermat.*, 45: 4, 1933.
8. Beecher, W. L. Canker sores in the mouth. Specific hypersensitiveness or allergy as a cause. *Clin. Med. & Surg.*, 35: 903, 1928.
9. Bennett, G. A., Zeller, J. W. and Bauer, W. Subcutaneous nodules of rheumatoid arthritis and rheumatic fever. A pathologic study. *Arch. Path.*, 30: 70, 1940.
10. Best, W. R., Kark, R. M., Muehrcke, R. C. and Samter, M. Clinical value of eosinophil counts and eosinophil response tests. *J. A. M. A.*, 151: 702, 1953.
11. Bjorneboe, M., Gormsen, H. and Lundquist, F. R. Further experimental studies on the role of the plasma cells as antibody producers. *J. Immunol.*, 55: 121, 1947.
12. Bjorneboe, M., Fischel, E. E. and Stoerck, H. C. The effect of cortisone and adrenocorticotrophic hormone on the concentration of circulating antibody. *J. Exper. Med.*, 93: 37, 1951.
13. Blumstein, G. L. and Johnson, J. Gastro-intestinal allergy simulating regional ileitis. *J. A. M. A.*, 147: 1441, 1951.
14. Bohrod, M. G. Classification of the histologic reactions in allergic diseases. *Am. J. Med.*, 3: 511, 1947.
15. Bohrod, M. G. Classification of the allergic tissue responses. *New York State J. Med.*, 51: 2746, 1951.
16. Broman, T. Pathogenetic problems in multiple sclerosis. Abstracts of Lectures and Communications, First International Congress (of Allergy), p. 77. Zurich, Sept. 23–29, 1951.
17. Brown, E. A. Drug allergy. *Quart. Rev. Allergy*, 7: 51, 1953.
18. Brown, E. A. The broad spectrum antibiotic agents and their untoward reactions. *Quart. Rev. Allergy*, 8: 526, 1954.
19. Brown, E. A. Problems of drug allergy. *J. A. M. A.*, 157: 814, 1955.
20. Corper, H. J., Cohn, M. L. and Stoner, R. E. *In vitro* phagocytosis. *Am. Rev. Tuberc.*, 46: 566, 1945.
21. Criep, L. H., Mayer, L. D. and Lozano-Menchaca, O. E. The effect of adrenalectomy on experimental hypersensitiveness. *J. Allergy*, 22: 314, 1951.
22. Davison, H. M. Allergy of the nervous system. *Quart. Rev. Allergy*, 6: 157, 1952.
23. Dick, G. F. and Leiter, L. Experimental amyloidosis and hyperglobulinemia. *Tr. A. Am. Physicians*, 52: 246, 1937.
24. Duke-Elder, S. Parsons' Diseases of the Eye. New York, 1954. Macmillan Co.
25. Dutton, L. O. Possible etiology of appendicitis. *Ann. Allergy*, 1: 17, 1943.
26. Dworetzky, M., Code, C. F. and Higgins, G. M. Effect of cortisone and ACTH on eosinophiles and anaphylactic shock in guinea pigs. *Proc. Soc. Exper. Biol. & Med.*, 75: 201, 1950.
27. Eagle, W. W. Lermoyez' syndrome—allergic disease. *Ann. Otol. Rhin. & Laryng.*, 57: 453, 1948.
28. Earle, D. P., Jr., Loeb, E. N., Seegal, D., Lyttle, J. D. and Jost, E. L. The serum antistreptolysin titer in chronic glomerulonephritis. The relation of the serum antistreptolysin titer to the exacerbation in chronic glomerulonephritis. *J. Clin. Investigation*, 21: 483, 491, 1942.
29. Editorial. Temporal arteritis; a new disease entity. *J. A. M. A.*, 131: 669, 1946.
30. Editorial. Migration for relief from allergies. *J. A. M. A.*, 154: 412, 1954.
31. Editorial. ACTH and cortisone in infection. *New England J. Med.*, 245: 75, 1951.
32. Ehrich, W. E., Drabkin, D. L. and Forman, C. Nucleic acids and the production of antibody by plasma cells. *J. Exper. Med.*, 90: 157, 1949.
33. Ehrich, W. E. and Glick, D. Immunity and hypersensitivity. Relation to disease in man, report of the 9th M & R Pediatric Research Conference (Oct. 30–31, 1953), M & R Laboratories, Columbus 16, Ohio, 1955.
34. Epstein, S. The antigen-antibody reaction in contact dermatitis. *Ann. Allergy*, 10: 633, 1952.
35. Fagraeus, A. The plasma cellular reaction and its relation to the formation of antibodies *in vitro*. *J. Immunol.*, 58: 1, 1948.
36. Fagraeus, A. Antibody production in relation to the development of plasma cells. *Acta med. Scandinav.*, supp. 204: 9–122, 1948.
37. Ferraro, A. Vascular changes in experimental anaphylaxis of the brain. *J. Neuropath. & Exper. Neurol.*, 4: 1, 1945.
38. Fischel, E. E. The relationship of adrenal cortical activity to immune responses. *Bull. New York Acad. Med.*, 26: 255, 1950.
39. Fog, T. On the pathogenesis of multiple sclerosis. (Report of the 11th Congress of Scandinavian Neurologists). *Acta psychiat. et neurol. scandinav.*, supp. 74: 22, 1951.
40. Gairdner, D. The Schönlein-Henoch syndrome. *Quart. J. Med.*, 66: 95, 1948.
41. Gell, P. G. H., Harrington, C. R. and Rivers, R. P. The antigenic functions of simple chemical compounds; Production of precipitins in rabbits. *Brit. J. Exper. Path.*, 27: 267, 1946.
42. Gell, P. G. H. and Hinde, I. T. Observations on the histology of the Arthus reaction and its relation to other known types of skin hypersensitivity, *Internat. Arch. Allergy*, 5: 23, 1954.
43. Germuth, F. G., Jr., Ottinger, B. and Oyama, J. Influence of cortisone on experimental hypersensitivity and circulating antibody in the guinea pig. *Proc. Soc. Exper. Biol. & Med.*, 80: 188, 1952.
44. Godlowski, Z. Z. Enzymatic Concept of Anaphyl-

axis and Allergy. Edinburgh and London, 1953. E. & S. Livingstone, Ltd.

45. Good, R. A. and Thomas, L. Studies on the generalized Shwartzman reaction. IV. Prevention of the localized and generalized Shwartzman reactions with heparin. *J. Exper. Med.*, 97: 871, 1953.
46. Gordon, G. L. The development of a refractory state to adrenocorticotropic hormone. *Endocrinology*, 45: 571, 1949.
47. Gordon, J. Z. and Thurber, D. C. Temporal arteritis. Report of a case and a comparison with respect to periarteritis nodosa. *Arch. Path.*, 42: 402, 1946.
48. Graña, A. Experimental purpura and pancreatic necrosis produced by Forssman heterophile antibody. *Proc. Staff Meet., Mayo Clin.*, 21: 298, 1946.
49. Gross, L. Cardiac lesions in Libman-Sacks disease. With consideration of its relationship to acute diffuse lupus erythematosus. *Am. J. Path.*, 16: 375, 1940.
50. Gudzent, F. Eiweissallergie and Gicht und Rheumatismus. *Ztschr. ges. inn. med.*, 6: 621, 1951.
51. Hardy, H. L. Delayed chemical pneumonitis in workers exposed to beryllium compounds. *Am. Rev. Tuberc.*, 57: 547, 1948.
52. Harkavy, J Hypersensitiveness to tobacco and biopsy studies of skin reactions in vascular disease. *J. Allergy*, 9: 475, 1938.
53. Harkavy, J. Allergic factors in gout. *J. A. M. A.*, 139: 75, 1949.
54. Harrington, W. J., Sprague, C. S., Minnich, V., Moore, C. V., Aulvin, R. C. and Dubach, R. Immunologic mechanisms in idiopathic and neonatal thrombocytopenic purpura. *Ann. Int. Med.*, 38: 433, 1953.
55. Hartman, M. M. The newer drugs for allergic disorders and their place in the histamine theory. *California Med.*, 66: 242, 1947.
56. Hartman, M. M. Aspermia as an allergic manifestation. To be published.
57. Haserick, J. R. and Bortz, D. W. New diagnostic test for acute disseminated lupus erythematosus. *Cleveland Clin. Quart.*, 16: 158, 1949.
58. Hass, G. M., Huntington, R. and Krumdieck, N. Amyloid. III. The properties of amyloid deposits occurring in several species under diverse conditions. *Arch. Path.*, 35: 226, 1943.
59. Jacques, L. B. and Waters, E. T. The isolation of crystalline heparin from the blood of dogs in anaphylactic shock. *Am. J. Physiol.*, 129: 389, 1940.
60. Kabat, E. A., Wolf, A. and Bezer, A. E. The rapid production of acute disseminated encephalomyelitis in Rhesus monkeys by injection of heterologous and homologous brain tissue with adjuvants. *J. Exper. Med.*, 85: 117, 1947.
61. Kampmeier, R. H. Vascular diseases due to hypersensitivity: socalled diffuse collagen disease. *Am. Pract. & Digest. Treat.*, 1: 113, 1950.
62. Kass, I., Jackson, A. and Slavin, M. Sarcoidosis: a hypersensitivity disease. *J. Allergy*, 25: 453, 1954.
63. Katz, G. and Cohen, S. Experimental evidence for histamine release in allergy. *J. A. M. A.*, 117: 1782, 1941.
64. Kay, C. F., Lucchesi, P. F. and Rutherford, R. B. An experimental investigation of an immunologic mechanism as the cause of glomerulonephritis. *J. Immunol.*, 42: 369, 1941.
65. Knowles, H. C., Zeek, P. M. and Blankenhorn, M. A. Studies on necrotizing angiitis. IV. Periarteritis nodosa and hypersensitivity angiitis. *Arch. Int. Med.*, 92: 789, 1953.
66. Koster, L. and Alers, C. J. Responses to heavy physical effort in patients with bronchial asthma and the resulting variations in the eosinophilic leukocyte counts. *Nederl. tijdschr. geneesk.*, 97: 940, 1953.
67. Kuttner, A. G. and Reyersbach, G. The prevention of streptococcal upper respiratory infections and rheumatic recurrences in rheumatic children by the prophylactic use of sulfanilamide. *J. Clin. Investigation*, 22: 77, 1943.
68. Lange, K., Gold, M. M. A., Weiner, D. and Simon, V. Autoantibodies in human glomerulonephritis. *J. Clin. Investigation*, 28: 50, 1949.
69. Landsteiner, K. The Specificity of Serological Reactions. Cambridge, 1945. Harvard University Press.
70. Larson, E. and Zoeckler, S. J. ACTH in Reiter's syndrome. *Am. J. Med.*, 14: 307, 1953.
71. Latta, H., Gitlin, D. and Janeway, C. A. Experimental hypersensitivity in the rabbit. The cellular localization of soluble azoprotein, injected intravenously. *Arch. Path.*, 51: 260, 1951.
72. Levy, B. The value of antihistamine drugs in the treatment of infective arthritis and Reiter's disease. *J. Roy. Army. M. Corps.*, 97: 93, 1951.
73. Lindsay, S., Aggeler, P. M. and Lucia, S. P. Chronic granuloma associated with periarteritis nodosa. *Am. J. Path.*, 20: 1057, 1944.
74. Long, D. A. and Miles, A. A. Opposite reactions of thyroid and adrenal hormones in allergic hypersensitivity. *Lancet*, 1: 492, 1950.
75. Lowell, F. C. Allergy to drugs and bacteria. *J. A. M. A.*, 136: 665, 1948.
76. Lucia, S. P., Hunt, M. and Bierman, H. R. The influence of antihistamine agents on erythrocyte agglutination and related phenomena. *J. Lab. & Clin. Med.*, 41: 574, 1953.
77. Madison, F. W. The role of allergy in pathogenesis of purpura and thrombocytopenia. *Blood*, 3: 1083, 1948.
78. Marcolongo, F. Favismo ittero-emoglobinurico. *Minerva med.*, 44: 1963, 1953.
79. Marrack, J. R. The biological significance of complete and incomplete antibodies. *Internat. Arch. Allergy*, 2: 264, 1951.
80. McPherson, S. D., Jr. and Woods, A. C. Significance of intracutaneous test for hypersensitivity to uveal pigment. *Am. J. Ophth.*, 31: 35, 1948.
81. Morgan, I. M. Allergic encephalomyelitis in monkeys in response to injection of normal monkey nervous tissue. *J. Exper. Med.*, 85: 131, 1947.
82. Murphy, G. E. and Swift, H. F. The induction of rheumatic-like cardiac lesions in rabbits by repeated focal infections with group A streptococci. Comparison with the cardiac lesions of serum disease. *J. Exper. Med.*, 91: 485, 1950.
83. Pinkus, H. Histopathology of allergic dermatoses. *Ann. Allergy*, 12: 671, 1954.

84. Rich, A. R. and Lewis, M. R. The nature of allergy in tuberculosis as revealed by tissue culture studies. *Bull. Johns Hopkins Hosp.*, 50: 115, 1932.
85. Rich, A. R. and Gregory, J. E. Experimental evidence that lesions with the basic characteristics of rheumatic carditis can result from anaphylactic hypersensitivity. *Bull. Johns Hopkins Hosp.*, 73: 239, 1943.
86. Rich, A. R. and Gregory, J. E. On the anaphylactic nature of rheumatic pneumonitis. *Bull. Johns Hopkins Hosp.*, 73: 465, 1943.
87. Rich. A. R. The Pathogenesis of Tuberculosis, Springfield, Ill., 1944. Charles C Thomas Co.
88. Rich, A. R. Hypersensitivity in disease with especial reference to periarteritis nodosa, rheumatic fever, disseminated lupus erythematosus, and rheumatoid arthritis. *Harvey Lect.*, series XLII: 106–147, 1946–1947. (Lecture delivered Nov. 21, 1946.)
89. Robertson, T. Extensive plasmacytosis and hypersensitive states. *New York State J. Med.*, 50: 2807, 1950.
90. Rocha e Silva, M. and Andrade, S. O. Histamine and proteolytic enzymes. Liberation of histamine by papain. *J. Biol. Chem.*, 149: 9, 1943.
91. Rocha e Silva, M. Anaphylatoxin and histamine release. *Quart. Rev. Allergy*, 8: 220, 1954.
92. Rose, B. and Brown, J. S. L. On the distribution and rate of disappearance of injected histamine in normal and adrenalectomized rats. *Am. J. Physiol.*, 123: 175, 1938.
93. Rose, B. Histamine, hormones and hypersensitivity. *J. Allergy*, 25: 168, 1954.
94. Rose, B., Fyles, T. W. and Venning, E. H. Corticotrophin, cortisone and hydrocortisone in diseases of hypersensitivity. I. Biological corticoid excretion during acute symptoms. *J. Allergy*, 26: 1, 1955.
95. Rytand, D. A. Fatal anuria, the nephrotic syndrome and glomerular nephritis as sequels of the dermatitis of poison oak. *Am. J. Med.*, 5: 548, 1948.
96. Sabin, F. R. Cellular reactions to a dye-protein with a concept of the mechanism of antibody formation. *J. Exper. Med.*, 70: 67, 1939.
97. Sack, S. S. Atopic cataract. *Ann. Allergy*, 5: 353, 1947.
98. Sands, J. H., Palmer, P. P., Mayock, R. L. and Creger, W. P. Evidence for serologic hyperreactivity in sarcoidosis. *Am. J. Med.*, 19: 401, 1955.
99. Shaw, C. C. ACTH, cortisone and hydrocortisone. Rationale of therapy. *Postgrad. Med.*, 15: 308, 1954.
100. Small, J. C. and Small, J. C., Jr. Bacterial allergy in the rheumatic diseases. *Ann. Allergy*, 11: 609, 1953.
101. Smoleroff, J. W. Scleral disease in rheumatoid arthritis. *Arch. Ophth.*, 29: 98, 1943.
102. Solomon, H. A. and Schwartz, S. Eosinophilic granuloma of bone. *J. A. M. A.*, 128: 729, 1945.
103. Steiner, K. Glomerulonephritis associated with atopic dermatitis *New England J. Med.*, 247: 20, 1952.
104. Stetson, C. A. and Good, R. A. Studies on the mechanism of the Shwartzman phenomenon. Evidence for the participation of polymorphonuclear leukocytes in the phenomenon. *J. Exper. Med.*, 93: 49, 1951.
105. Storck, Von H., Bigliardi, P., Brenn, H. and Hoigne, R. Über die Bedeutung der Thrombocyten bei allergischen Vorgängen. *Schweiz. med. Wchnschr.*, 83: 692, 1953.
106. Szilard, Z., Rauss, K. and Szabo, I. New viewpoints in the pathogenesis and therapy of chronic cholecystitis. *Internat. Arch. Allergy*, 2: 160, 1951.
107. Tallroth, A. On regional enteritis with special reference to its etiology and pathogenesis. *Acta chir. Scandinav.*, 88: 407, 1943.
108. Teilum, G. Allergic hyperglobulinosis and hyalinosis (paramyloidosis) in the reticulo-endothelial system in Boeck's sarcoid and other conditions. A morphologic immunity reaction. *Am. J. Path.*, 24: 389, 1948.
109. Teilum, G. Hyperglobulinemia, periarterial fibrosis of the spleen, and the wire loop lesion in disseminated lupus erythematosus in relation to allergic pathogenesis. *Am. J. Path.*, 24: 409, 1948.
110. Thal, A. and Brackney, E. Acute hemorrhagic pancreatic necrosis produced by local Shwartzman reaction. *J. A. M. A.*, 155: 569, 1954.
111. Thomas, J. W. Ocular manifestations of allergy. *Ann. Allergy*, 12: 1, 1954.
112. Thomas, L. and Good, R. A. The effect of cortisone on the Shwartzman reaction. The production of lesions resembling the dermal and generalized Shwartzman reactions by a single injection of bacterial toxin in cortisone-treated rabbits. *J. Exper. Med.*, 95: 409, 1952.
113. Tullis, J. L. Platelet antibody tests in the diagnosis of purpura. *New England J. Med.*, 249: 591, 1953.
114. Waldbott, G. L. So-called thymic death. VI. The pathologic process in 34 cases. *Am. J. Dis. Child.*, 47: 41, 1934.
115. Weinberg, T. Periarteritis nodosa in granuloma of unknown etiology. *Am. J. Clin. Path.*, 16: 784, 1946.
116. Wesslen, T. Passive transfer of tuberculin hypersensitivity by viable lymphocytes from the thoracic duct. *Acta tubers. Scandinav.*, 26: 38, 1952.
117. Wiener, A. S. The solution of certain fundamental immunological problems by studies of Rh sensitization. *Ann. Allergy*, 10: 535, 1952.
118. Wilson, K. S. and Alexander, H. L. The relationship of periarteritis nodosa to bronchial asthma and other forms of human hypersensitiveness. *J. Lab. & Clin. Med.*, 30: 195, 1945.
119. Winer, L. H. Histopathology of the nodose lesions of the lower extremities. *Arch. Dermat. & Syph.*, 63: 347, 1951.
120. Wright, C. S., Dodd, M. C., Bouroncle, B. A., Doan, C. A. and Zollinger, R. M. Studies of hemagglutinins in hereditary spherocytosis and in acquired hemolytic anemia: their relationship to the hypersplenic mechanism. *J. Lab. & Clin. Med.*, 37: 165, 1951.
121. Ehrich, W. E. The functional significance of the various leukocytes in inflammation. *J. Mt. Sinai Hosp.*, 15: 337, 1949.

122. Tompkins, E. H. The response of monocytes to adrenal cortical extract. *J. Lab. & Clin. Med.*, 39: 365, 1952.
123. Code, C. F., Mitchell, R. G. and Kennedy, J. C. The effect of cortisone on the number of circulating basophiles and eosinophils: is there a relationship between these cells? *Proc. Staff Meet., Mayo Clin.*, 29: 200, 1954.
124. Speirs, R. S. Physiological approaches to an understanding of the function of eosinophiles and basophiles. *Ann. New York Acad. Sc.*, 59: 706, 1955.
125. Oliver, J., Bloom, F. and Mangieri, C. On the origin of heparin. An examination of the heparin content and the specific cytoplasmic particles of neoplastic mast cells. *J. Exper. Med.*, 86: 107, 1947.
126. Holmgren, H. and Wilander, O. Beitrag zur Kenntnis der Chemie und Funktion der Ehrlichschen Mastzellen. *Ztschr. f. mikr. anat. Forsch.*, 42: 242, 1937.
127. Riley, J. F. and West, G. B. The presence of histamine in tissue mast cells. *J. Phiysol.*, 120: 528, 1953.
128. Riley, J. F. Pharmacology and functions of the mast cells. *Pharmacol. Rev.*, 7: 267, 1955.
129. Fawcett, D. W. Cytological and pharmacological observations on the release of histamine by mast cells. *J. Exper. Med.*, 100: 217, 1954.
130. Valentine, W. N., Lawrence, J. S., Pearce, M. L. and Beck, W. S. Relationship of the basophil to blood histamine in man. *Blood*, 10: 154, 1955.
131. Graham, H. T., Lowry, O. H., Wheelwright, F., Lenz, M. A. and Parish, H. H., Jr. Distribution of histamine among leukocytes and platelets. *Blood*, 10: 467, 1955.
132. Vercauteren, R. The properties of the isolated granules from blood eosinophils. *Enzymologia*, 16: 1, 1953.
133. Sicuteri, F. and Zurlo, A. Changes in the eosinophilic content of blood due to histamine in Addison's disease. *Folia Allergol.*, 1: 396, 1954.

Seminar on Diseases of the Pancreas

Exocrine Pancreatic Secretion*

Effects of Pancreatic Disease

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DURING the past decade notable progress has been made in clarifying the basic mechanisms of pancreatic physiology. These advances for the most part have been derived from studies that have elucidated the factors controlling the secretion of pancreatic juice, from anatomico-physiologic investigations of the gland secreting under normal and abnormal conditions, and from precise physiochemical analyses of the pancreatic juice itself. The data thus amassed, supplemented by contributions from the radiologists and surgeons, when applied to the problems of pancreatic disease, have resulted in better understanding of the pathogenesis of pancreatic inflammation, in more exact and reliable diagnosis of pancreatic affections and, through utilization of therapeutic measures directed against specific etiologic mechanisms, in more rational and efficacious treatment of pancreatic disease. It is the purpose of this review to present the modern concepts of the essential physiology of the normal and abnormal exocrine pancreas.

EXOCRINE PANCREATIC SECRETION

Regulation of Pancreatic Secretion. Pancreatic juice as it appears in the duodenum consists of water, electrolytes and a protein moiety of digestive ferments. The fluid is colorless, of low viscosity, alkaline (pH about 8.3) and includes the inorganic ions Na^+, K^+, HCO_3^- and Cl^-. Ca^{++}, Zn^{++}, $HPO_4^=$ and $SO_4^=$ are present in lesser concentrations.

Secretion of pancreatic juice is continuous in some species and intermittent in others; in man, secretion appears to be continuous,[1] although this has not yet been proved. During digestion, secretion is augmented by the factors which regulate pancreatic flow, namely hormonal, neurogenic and vascular factors.

The hormones regulating pancreatic flow are secreted in the duodenum and upper jejunum in response to stimulation by hydrochloric acid, fats, proteins, carbohydrates and partially digested foodstuffs. These hormones are absorbed by the portal system and transported through the bloodstream to the pancreas, liver and gallbladder where their secretory effects are exerted directly. Bayliss and Starling[2] were able to extract these active secretogogues from the duodenal mucosa as an amorphous powder which they named "secretin." This crude secretin has been fractionated into five component hormones: (1) secretin proper which incites the flow of a thin, watery fluid of high bicarbonate concentration and low enzyme content,[3] (2) pancreozymin which stimulates excretion of a viscid, low bicarbonate, high enzyme pancreatic juice,[4] (3) hepatocrinin which causes the elaboration of a thin, water, salt-poor, biliary flow,[5] (4) cholecystokinin which induces contraction and emptying of the gallbladder,[6] and (5) enterocrinin which stimulates the flow of succus entericus.[7]

The segregation of activity of the various components of the secretin complex was accomplished by study of the secretory effects of purified preparations. Mellanby[3] demonstrated that secretin proper was responsible for the water and bicarbonate secretion of the pancreas and the vagal stimulation, although not augmenting either flow or alkalinity of the juice, evoked a large outpouring of pancreatic enzymes. On the other hand, enzyme concentration following intravenous injection of purified secretin was found to decline inversely as the volume flow was

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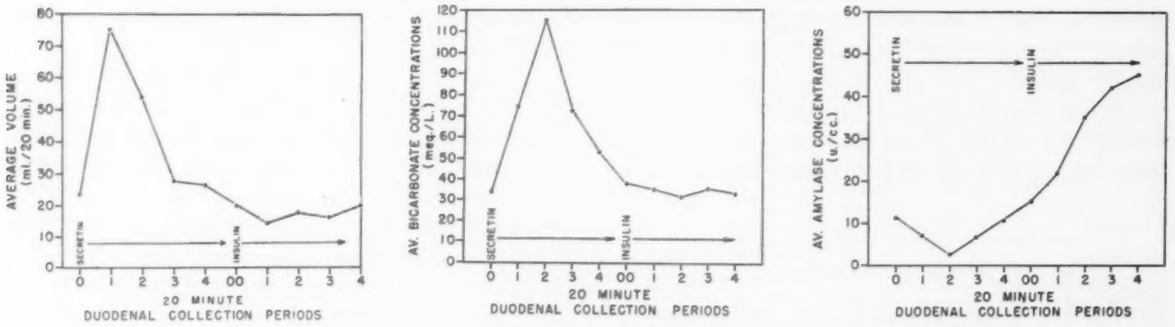

FIG. 1. The volume, bicarbonate and enzyme responses of the pancreas to hormone stimulation (secretin) and nervous stimulation (vagal-insulin hypoglycemia).

increased. (Fig. 1.) It was apparent that, if crude secretin elicited an enzyme response which purified secretin did not, some principle had been lost in preparation. Harper and Raper[4] have shown this moiety to be pancreozymin which, when administered parenterally, only minimally affects the rate of fluid formation and bicarbonate secretion but markedly stimulates the rate of enzyme elaboration. Some evidence exists that secretory fibers in the vagus and sympathetics may potentiate the action of both secretin and pancreozymin.[8,9a,9b] Denervation of the pancreas, presumably by increasing pancreatic blood flow, has also been shown by Wang and Grossman[10] to augment the formation of enzymes in response to pancreozymin.

The nervous control of pancreatic secretion has both sympathetic and parasympathetic components. Vagal stimulation with insulin hypoglycemia has been shown experimentally[11] and has been shown in clinical studies of patients before and after vagisection[12,13] to increase enzyme secretion but not flow or bicarbonate. (Fig. 1.) The effect of the sympathetic nerves is not so clearly defined.[14] In the experimental animal slight decrease in flow can be observed following sympathetic stimulation[15] but some augmentation of flow is also seen after splanchnic section.[16] In addition, the splanchnics contain motor fibers which appear to increase the secretion of enzymes, as was noted by potentiation of pancreozymin activity.[17] Kuntz and Richins[18] have harmonized this disparate finding by postulating that the effect of sympathetic stimulation on the pancreas is a summation of motor and inhibitory actions on the acinar parenchyma superimposed upon the secretory changes produced by alterations in blood flow to the glandular substance. In general, decreases in pancreatic blood flow tend to diminish pancreatic secretory activity; augmentation of flow has the reverse effect. Finally, there is some evidence that pancreatic secretory fibers in the sympathetic components may be the effector pathway of a motor reflex arc initiated in the duodenum by the mechanical and chemical stimulation of foodstuffs.[1]

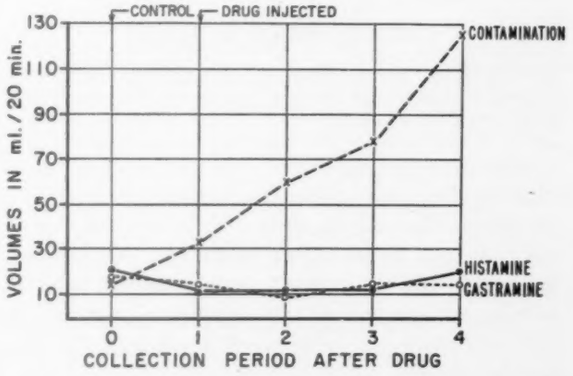

FIG. 2. Volume response of pancreas to drugs which stimulate gastric acid production in patients in whom acid is permitted to enter the duodenum (contamination) and in those in whom it is not permitted so to do (histamine, gastramine).

The augmentation of pancreatic secretion during digestion thus has been shown to result from stimuli arising within the duodenum and acting via hormone and nerve mechanisms. The specific stimuli comprise the contents of gastric chyme, namely, hydrochloric acid, protein, the products of protein digestion, the products of carbohydrate digestion, fat, and the products of fat digestion. Each of these substances when studied experimentally is capable of evoking a characteristic type of pancreatic secretion.[1] Hydrochloric acid directly, and drugs such as histamine[19] or alcohol[20] (which stimulate gastric acid secretion) indirectly (Fig. 2), produce a watery alkaline

secretion low in enzyme activity (secretin-type juice). The carbohydrates, although not able to induce secretion in the resting gland, moderately augment the enzyme output of the actively secreting pancreas.[21] On the other hand, protein and fats, as well as their intermediate products

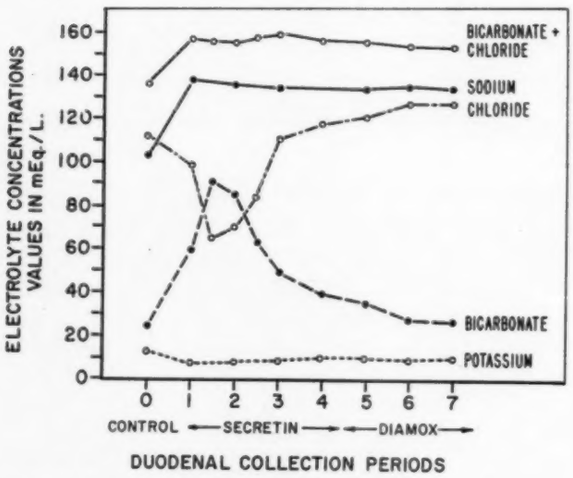

FIG. 3. Electrolyte secretion of the pancreas under conditions of stimulation of flow by secretin and inhibition of secretion by diamox.

of digestion, are powerful stimuli for enzyme secretion but affect only minimally the production of fluid (pancreozymin-vagal type secretion). It has been shown recently that enterogastrone exerts an inhibitory action on the secretogogue effects of foodstuffs in the duodenum.[22]

It is of interest to note that, despite the extensive study of the regulation of pancreatic secretion during the past fifty years, the relative importance of the nerve and humoral factors in human digestion remains just as much an unresolved physiologic problem as it was in the early 1900's when the controversy was initiated between the adherents of a hormone mechanism of Bayliss and Starling[2] and the advocates of the nerve mechanism of Pavlov.[23] Today both these are still tenable,[24] indeed Thomas has formulated a concept which combines both mechanisms.[1] The hormone factor, secretin, is credited with the maintenance of homeostasis (alkalinity) in the duodenum in order to provide an optimal medium for the action of the pancreatic ferments. The nerve mechanism, including local duodenopancreatic reflexes, is believed to be of greater significance in the regulation of pancreatic enzyme secretion during human digestion.

Mechanisms of Pancreatic Secretion. Until recently, very little was known concerning the basic mechanisms of secretion in the pancreas. Morphologic evidence and data obtained from experimental studies with substances such as ethionine[25] and alloxan,[26] which selectively destroy specific types of parenchymal cells, have indicated that the digestive enzymes are secreted by the acinar cells while fluid and bicarbonate are secreted from the intralobular duct cells.[24] This differentiation of cellular function, although by no means proved, is strongly supported by the clinical evidence of the dissociation of bicarbonate and enzyme responses to secretin which have been noted in chronic pancreatitis by Friedman[27] and Dreiling.[28]

The secretion of electrolytes by the human pancreas is in the form of a solution isotonic to the blood plasma despite variations in flow and under conditions of stimulation or inhibition of secretion.[29] (Fig. 3.) The concentrations of the cations Na^+, K^+ and Ca^{++} approximate the diffusible ionic content of the blood plasma. Although the total anion concentration remains constant under all conditions of secretion, the Cl^- content varies inversely with the concentration of HCO_3, the latter increasing as the rate of secretion increases.[30] Studies with diamox,® a potent carbonic anhydrase inhibitor, have demonstrated that the secretion of bicarbonate appears to be under the catalytic influence of carbonic anhydrase which controls the formation of the bicarbonate ion within the cell according to the equation:[31]

$$H_2O + CO_2 \rightleftarrows H_2CO_3 \rightleftarrows H^+ + HCO_3^-$$

Diamox, by blocking the catalysis of the preceding reaction, was shown to be capable of inhibiting the total fluid and total bicarbonate responses to secretin without noticeably affecting the concentration of bicarbonate within the secretion. (Fig. 4.) Such a relationship strongly supports the thesis advanced by Hollander[32] of the elaboration by the pancreatic secretory cells of a fluid of fixed bicarbonate content.

The secretion of enzymes by the pancreas involves a synthesis of these proteins within the acinar cells, their aggregation as zymogen granules, and some process whereby they are discharged into the ducts and into the blood stream. Little is known concerning the mechanisms of enzyme formation except that the high

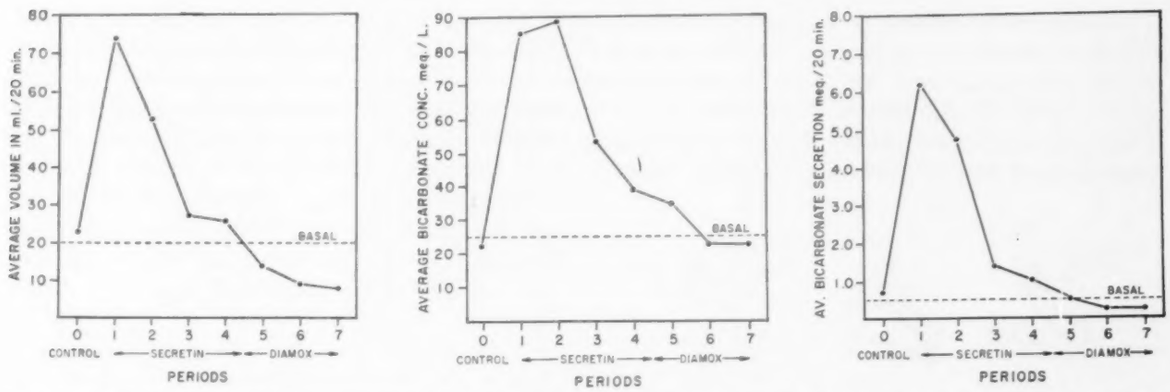

FIG. 4. The volume, bicarbonate concentration and bicarbonate rate of secretion following stimulation by secretin and inhibition by diamox in patients without disease of the pancreas.

rate of protein turnover within the pancreas is correlated with enzyme synthesis. Deficiencies in protein metabolism, clinically[33] and under controlled experimental regimens,[34] have been shown to diminish enzyme secretion. The dietary substitution of ethionine for its analog, the essential amino acid methionine, not only leads to cessation of enzyme synthesis but also to disruption of the secretory acinar cells; moreover, these effects can be prevented by administration of methionine.[35]

The elaboration of ferment in response to all known stimuli appears to occur in parallel fashion for each individual pancreatic enzyme both in normal function and in diseased states of the pancreas.[4,36,37] The enzymes formed are discharged either by diffusion or by some process of secretion from the acinar cells into the duct system and thence into the blood stream. "Endocrine" secretion occurs in the pancreas as it has been observed to do for other exocrine digestive enzymes.[38] The factors in the pancreas which control this partition of enzyme between endocrine and exocrine secretion are not completely understood. In the stomach a good correlation exists between the rate of secretion of gastric pepsin and the rate of its discharge into the blood as measured by uropepsin; however, neither increases in volume flow of pancreatic juice nor stimulation of pancreatic enzyme production *per se* cause an elevation of the pancreatic ferments in the serum.[40] On the other hand, stimulation of pancreatic flow in the presence of obstruction of the pancreatic ducts,[41] stimulation of pancreatic enzymes in the presence of obstruction to flow[42] and, finally, a rise in intraductal pressure[43–45] cause an elevation of the serum enzymes, apparently by a process of hydrostatic diffusion from the duct system into the tissue spaces and thence into the blood stream.[40]

The pancreatic ferments found in the blood stream include amylase, which is in the active state, and lipase, which occurs in inactive form. Trypsin cannot be demonstrated in blood serum because of the presence of potent protease inhibitors. Endocrine secretion of trypsin is deduced from alterations in the serum antiproteolytic activity,[46] fibrinogen content,[47] and blood coagulability,[48] which attend extirpation of the pancreas,[49] acute inflammatory disease,[50] and parenteral administration of active trypsin.[51] Innerfield believes that trypsin normally secreted by the pancreas into the blood stream is an essential element in the equilibrium between the thrombinogen and anticoagulant factors maintaining normal coagulability of the blood.[52]

Pancreatic Outflow Tract. The pancreatic juice is conveyed by a duct system the anatomic arrangement of which has incited much comment since the enunciation of the "common channel theory" of pancreatitis by Opie.[53] There are two collecting ducts, the major or duct of Wirsung which enters the duodenum in close association with the choledochus at a common orifice, the papilla of Vater, and the minor duct or duct of Santorini which joins the duodenum at a separate opening cephalad to the papilla. Considerable variability exists in the arrangement and communication between the major and minor pancreatic ducts and the frequency with which the major duct terminates with the choledochus in a common chamber, the ampulla of Vater, permitting free association of bile and pancreatic juice prior to discharge through the papilla into the duodenum.[54]

Regulation of the flow of bile and pancreatic juice into the duodenum is under the control of a physiologic sphincter[55] the function of which appears to be the summation of the tonic action of circular smooth muscle fibers at the papilla of Vater around the common opening of both ducts

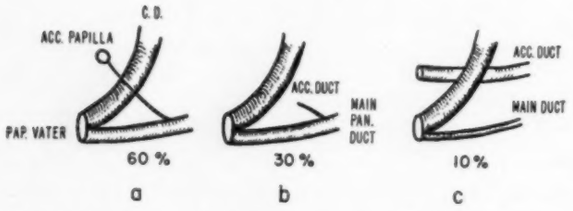

FIG. 5. Anatomic relations of common duct, main pancreatic duct (Wirsung) and accessory pancreatic duct (Santorini). After Kleitsch. a, Main pancreatic and common ducts join prior to entry into duodenum at papilla of Vater; accessory duct communicates with main duct and enters duodenum at separate papilla. b, Main pancreatic duct and common duct join prior to entry into duodenum at papilla of Vater; accessory duct communicates with main duct but does not enter duodenum separately. c, Accessory duct drains major part of pancreas and does not communicate with vestigial main pancreatic duct; pancreatic flow is completely separated from the biliary flow.

adjoining fibers which surround separately the anatomic terminations of both the main pancreatic duct and the common duct itself and, finally, the intrinsic musculature of the duodenum which has a pinchcock action due to the obliquity with which it is penetrated by the ampulla of Vater.[54] The tone of this complex sphincter is under hormonal influence,[6] neurogenic control,[56] and is responsive to chemical[57] (particularly hydrochloric acid[58]) and mechanical stimuli from the duodenum.[58] Sphincter tone also may be increased directly by a number of pharmacologic agents such as morphine and its derivatives,[59] parasympathomimetic drugs[60] and thorazine,[61] and by substances such as alcohol[59] which stimulate the flow of gastric acid and irritate the duodenal mucosa.

Much has been written concerning the frequency of the common channel in man. The reports ranging in incidence from 20 per cent[62] to 76 per cent[63] attest to the great variability of anatomic configuration in this area and to differences in interpretation of structural relationships.[64] Recently, two observers,[65,66] by careful injection and dissection technics in unselected postmortem material, have concluded that the anatomic configuration of a common channel has an incidence of between 30 per cent and 40 per cent. Sterling,[65] however, pointed out that the anatomic common channel is not synonymous with and should not be confused with the phenomenon of intraductal reflux, which he concluded was possible in only 17 per cent of his cases. Kleitsch,[66] moreover, stressing the importance of the accessory duct in the drainage of pancreatic juice, showed (Fig. 5) that the duct of Santorini accounted for almost the entire drainage of the gland in 10 per cent of the cases (c), partially drained the pancreas in another 60 per cent (a), and in the remaining 30 per cent of the cases, wherein it was merely a branch of the main duct, no separate communication with the duodenum was made (b). It was only in the latter group, Kleitsch concluded, that the dynamics of a common channel with intraductal reflux could be operative.

Investigation of the secondary assumption of the common channel hypothesis, reflux of bile into the pancreatic duct system, has resulted in careful study of the secretory pressures in the pancreatic tree and their relationship to the pressure gradients in the biliary tract. Early investigators,[60,67,68] impressed by the "bile factor" in pancreatitis,[62] planned studies which included the determination of (1) hydrostatic pressures necessary to overcome the resistance of the sphincter of Oddi when stimulated by intraduodenal hydrochloric acid or morphine, and hydrostatic pressures in the common duct necessary to produce reflux into the pancreatic ducts; (2) pressures in the common duct following contraction of the gallbladder and following cholecystectomy; (3) maximum secretory pressures attained in the occluded common and pancreatic ducts after stimulation by feeding and by drugs; and (4) the hydrostatic pressures necessary to cause rupture of the finer radicals of the pancreatic duct system when fluids are forcibly injected into the main pancreatic duct. The results of these studies are summarized in Table 1. Although the technics employed were unphysiologic, the general conclusion was that the pressure gradients in the pancreatic and common duct systems would not favor the retrograde passage of bile into the pancreatic duct and would favor pancreatic reflux into the biliary tree.[68] Parry[69] and others[70] have repeated these experiments under conditions more applicable to flow in the intact systems. By simultaneously measuring secretory pressures in unobstructed biliary and pancreatic ducts and in hydrostatic pressures in the duodenum, they

TABLE I

PRESSURE RELATIONSHIPS IN THE BILIARY AND PANCREATIC TRACTS DURING THE INTERSECRETORY PHASE AND FOLLOWING STIMULATION

	Pressure Determinations with Occlusion Technics				Pressure Determinations with Open Duct Technics (Parry)			
	Resting Pressures (mm. H_2O)		After Meals or Stimulation (mm. H_2O)		Resting Pressures (mm. H_2O)		After Meals or Stimulation (mm. H_2O)	
	Range	Average	Range	Average	Range	Average	Range	Average
Hepatic ducts	.....	...	200–300	...	.....	...	.....	...
Common duct	60–70	50	75–150	...	3–94	48	86–178	100
Common duct (postcholecystectomy)	.....	190	.....	...	.....	...	.....	...
Sphincter resistance	90–420	150	.....	...	110–135	75	.....	...
Gallbladder tonus	100–300	250	.....	350	.....	170	.....	...
Pancreatic ducts	.....	...	300–500	300	80–180	91	109–243	198
Rupture pressure	300–800	...	.....	...	.....	...	.....	...
Pressure necessary for biliary reflux	200–420	...	.....	...	.....	...	.....	...

have shown that the previously determined values were too high (Fig. 6) but that the original conclusions were still valid, namely, that the secretory pressures in the pancreatic duct were consistently higher than those found in the biliary tract while the subject was in the resting state and after meals and following specific stimulation of biliary and pancreatic flow.

Pancreatic Enzymes. In addition to its mineral constituents, previously discussed, the pancreatic secretion as it appears within the duodenum contains mucus, mucoproteins and the protein moiety of enzymes.[32] The pancreatic ferments, although classically described as three in number (amylase, lipase and trypsin) actually consist of two amylases (alpha and beta amylase),[71] a single lipase, four proteolytic enzymes, trypsin, chymotrypsin,[72] a peptidase,[73] a collagenase,[74] and other factors not yet isolated.

The amylases, secreted in active form, are responsible for the digestion of starch, glycogen and other carbohydrates to the disaccharide state from which further splitting is accomplished by the intestinal juice. Disaccharides and monosaccarides are absorbed directly or combined with phosphate by the intestinal mucosa.

Lipase accomplishes the degradation of fats to glycerol, fatty acids and monoglycerides, in which form, in combination with bile salts and the phosphate ion with which these unite, absorption occurs.

The proteolytic enzymes initiate protein digestion and continue the proteolysis begun in the stomach by pepsin, reducing the proteins to dipeptides and longer polypeptides. Further splitting produces amino acids which are absorbed as such by the intestinal mucosa. Trypsin and chymotrypsin are not secreted in the active state but rather in combination with specific enzyme inhibitors.[75] Some active trypsin and chymotrypsin is usually found in pure pancreatic

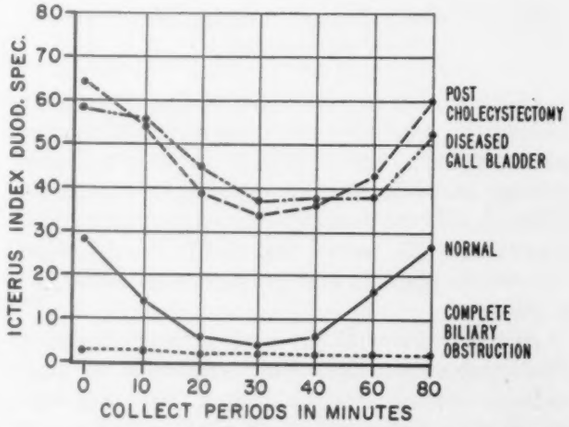

FIG. 6. Biliary pigment response (icterus index) data following secretin in patients who have and who do not have disease of the biliary tract.

juice,[75] and increased percentages have been reported in experimental pancreatitis, ethionine-induced pancreatitis,[76] and clinically in acute pancreatitis in humans.[77] The activation of these proteolytic enzymes is accomplished by the enzymatic action of free trypsin and by the action of the intestinal hormone, enterokinase,[72] which antagonizes the naturally occurring protein enzyme inhibitors in pancreatic juice.

The diversion or exclusion of pancreatic juice from the digestive tract by fistula formation or by total extirpation of the pancreas produces a number of metabolic derangements which previously were considered lethal but now, from observations in patients who have undergone pancreatectomy for carcinoma, are known to be compatible with life.[78] These metabolic derangements may be summarized as follows: (1) interference with carbohydrate metabolism—diabetes due to loss of islet function; (2) disturbances in electrolytic balance, especially when a fistula is present, due to losses of Na^+, Cl^- and HCO_3^-; (3) alteration in lipid metabolism, including a decline in blood lipids, loss of body fat, fatty degeneration of the liver and impairment of liver function, presumed to result from a "lipocaic" deficiency[79] or, more likely, from a deficiency of choline; and (4) serious impairment of digestive function due to loss of the necessary enzymes. The digestive defect is less marked for carbohydrates, more marked for proteins, and most marked for fats. It may be masked in part by a high carbohydrate, high protein, low fat diet, under which regimen the amylases, pepsin and peptidases of the small intestine are sufficient to maintain digestion.

EFFECTS OF PANCREATIC DISEASE ON EXOCRINE SECRETION

Disease of the pancreas, inflammatory or neoplastic, produces alterations in the exocrine pancreatic secretion. These may be reflected in characteristic abnormalities in (1) digestive capacity, (2) enzyme concentrations in the blood and urine, (3) blood coagulability and blood coagulation factors and (4) pancreatic secretory capacity.

Abnormalities in Digestive Capacity. Changes in stool composition: Disordered digestion in pancreatic disease is manifested by diarrhea, steatorrhea and/or azotorrhea. Simple diarrhea due to unexplained rapid transit time may precede more specific indications of external pancreatic secretory deficiency. The fat bulky stools observed in patients with pancreatic disease are due to this insufficient secretion of enzymes for digestion of protein and especially of fat. Therefore, in order to obtain quantitative data, stool analysis should be performed after administration of a high fat diet, the Schmidt regimen, for three days.[80] The stool is examined microscopically for undigested protein fibers and fat globules and determinations are made of dry weight and the content of total fat, fatty acids, neutral fat and nitrogen.

Stool examination gives information not only as to the completeness of digestion but also as to the extent of absorption of foodstuffs. Incomplete enzymatic digestion is reflected in bulky stools with a dry weight, which may be more than five times that of average, and also in a high content of nitrogen, total fat and neutral fat, fatty acids being low. Incomplete absorption is indicated by high nitrogen, high total fat, high fatty acid and low neutral fat stool concentrations. Theoretically such a differentiation is sound; in practice, however, the findings may be obscured by variations in bacterial digestion and in intestinal transit time which affect both completeness of digestion and extent of absorption. When the transit time is rapid, pancreatic steatorrheas cannot be differentiated by stool analyses from the non-pancreatic disorders such as sprue, celiac disease and other gastrointestinal disorders.[81–83]

Although daily excretion of more than 12 gm. of fat and 3 gm. of protein in patients on a high fat diet has been taken by some to indicate pancreatic digestive deficiency,[80,84] such marked changes are to be expected only in advanced stages of disease of the pancreas. Masking of pancreatic digestive deficiency is due to the tremendous reserve digestive capacity of the gland, to bacterial fermentation and to the accessory action of the intestinal and peptic enzymes; these variables render stool analysis an unsatisfactory and insensitive test of pancreatic function.[83]

Some attempts have been made to identify pancreatic insufficiency by measuring stool ferments. The proteolytic effect of a fecal suspension on a gelatin emulsion (x-ray film) has been widely employed as an assay of fecal tryptic content.[85] Such a test is of limited value save in congenital cystic fibrosis in which the enzyme deficiency is complete in most instances. Even in these patients false positive reactions occur be-

cause of bacterial gelatinases; however, the incidence of resulting errors may be decreased by special dilution technics or by addition to the fecal suspension of soybean trypsin inhibitor which antagonizes pancreatic trypsin but does not affect bacterial gelatinases.[85]

Alterations in digestive tolerance: Because of the unreliability of the results of the stool examination and the lack of sensitivity of the test in minimal pancreatic digestive deficiencies, a number of tolerance tests have been developed to estimate pancreatic function by analysis of various products of digestion in the stool, in the blood and in the urine following administration of a special meal. The first such procedure was the gelatin tolerance test. In this test the blood amino acid level is determined before and at hourly intervals after oral administration of 100 gm. of gelatin.[86] Flat curves have been noted in children with fibrocystic disease but not in persons with celiac disease.[87] In order to interpret the results with any assurance, the possibility of defective absorption must be eliminated by a complementary study of blood amino acid nitrogen after administration of glycine.[87] Althausen and Uyeyama[88] have investigated the value of the gelatine tolerance test in adults in whom disease of the pancreas was suspected and have not found it to be a reliable test of pancreatic function.

A starch tolerance test was therefore proposed by these investigators.[267] In this procedure the blood sugar curve following ingestion of 100 gm. of glucose is compared with a corresponding curve obtained by substituting 100 gm. of soluble starch. From criteria established by study of data in patients who do not have disease of the pancreas, Althausen and Uyeyama obtained abnormal responses in 87 per cent of patients with proved cancer of the pancreas or chronic pancreatitis and in 60 per cent of patients with suspected disease of the pancreas. The abnormal response was characterized by a relatively smaller rise in blood sugar after starch than after glucose, indicating lack of starch digestion. However, Kalser and his associates, from a careful study comparing the reliability of several diagnostic procedures in patients who had and who did not have disease of the pancreas, have concluded that the starch tolerance test is somewhat non-specific and less efficient than other methods.[89]

Protein digestion and absorption have been tested by the use of meals containing isotope-labeled proteins. Chinn et al.[90] used serum albumin tagged with radioactive I-131. Fecal and urinary excretion of the I-131 was measured for seventy-two hours following ingestion of the protein. Fecal excretion of the radioiodine was found to be higher in patients with disorders of the pancreas than in those with non-pancreatic digestive disturbances. This excretion was observed to be reduced upon administration of pancreatin. The same observers[91] also found this procedure to be useful in the diagnosis of cystic fibrosis of the pancreas. Shingleton et al.,[92] employing a similar test meal, gelatine containing I-131 tagged serum albumin, measured the serum radioactivity instead of the fecal excretion. Flat curves were obtained in patients with carcinoma of the pancreas and chronic pancreatitis but reservations as to the usefulness of the procedure were held: the test will not disclose minimal changes, intestinal transit must be checked by barium meal and abnormalities in absorption must be excluded by other means.

Fat and vitamin A tolerance tests have been used in the steatorrheas to differentiate sprue from pancreatic disease.[93] In these, the concentration of fatty acid and vitamin A in the blood are studied following administration of a test meal containing peanut oil and vitamin A. In pancreatic steatorrhea the fatty acid curve is flat but the vitamin A curve shows a normal rise, indicating enzyme deficiencies but not an absorption defect; in sprue both fatty acid and vitamin A curves are flat, directing attention to the basic absorption defect. Shingleton[92] using glycerol trioleate and Silverman[94] employing tagged lipiodol have demonstrated that fat tolerance tests have some value as screening procedures in diagnosing disorders of the pancreas. Nardi[95] studied the rate of synthesis of plasma phospholipid following administration of radioactive phosphate. In patients with disease of the pancreas a diminished synthesis was noted as evidenced by a lower level of plasma phospholipid than that observed in normal subjects.

Abnormalities in Blood and Urinary Pancreatic Ferment Concentrations. Blood enzyme levels: Determinations of pancreatic ferment concentrations in the blood are the most commonly employed and useful laboratory diagnostic procedures in general use. Serum amylase is the most conveniently measured enzyme. The amylase normally present in the blood is

derived from the pancreas, the salivary glands and the liver.[96] Some evidence is present that the normal amylase blood level is under endocrine control.[97] Decreases in blood amylase have been observed under conditions of adrenocortical stress,[98] in hepatocellular disease,[99] and in advanced pancreatic parenchymal destruction.[100] The increases in serum amylase content noted during the course of acute inflammations of the pancreas and/or ductal obstruction is derived wholly from the pancreas, either by retrograde passage due to back pressure[101] or by some alteration in cellular permeability or orientation of enzyme secretion.[38]

Elevations of the serum amylase above the statistically determined normal range occur during the first seventy-two hours of illness. In the milder inflammations small rises may be present for only a few hours, making it imperative for early and frequent amylase determinations during the initial period of illness. Not infrequently a drop to the normal range may take place rapidly, indicating early resolution. On the other hand, sudden decreases in serum amylase may reflect extensive destruction of the pancreas with subsequent cessation of enzyme production.[98,102] For these reasons it is not possible to correlate the severity of disease with the degree of elevation of blood amylase, nor does a normal amylase level exclude a diagnosis of disease of the pancreas.[100]

Blood amylase elevations have been reported in a number of situations in which no pancreatic affection is present.[103] These include acute disease of the gallbladder,[104] choledocholithiasis,[104] biliary dyskinesia,[105] perforated peptic ulcer,[106] uremia,[107] after cholangiography,[44] and after administration of morphine-like narcotics and parasympathomimetic drugs.[108] The physiologic mechanisms responsible for these elevations have been elucidated in part. In uremia the blood amylase rise is due to diminished excretion in the urine; concomitant renal insufficiency, in fact, may be responsible for persistent elevation in patients who have acute pancreatitis.[109] The elevations of blood amylase in extrapancreatic disease and following medication, although disquieting, are minimal in degree, and rare in occurrence; they hardly detract from the general usefulness of amylase determinations.[100,110]

Serum lipase elevations tend to parallel blood amylase rises but lipase increases occur later in the course of acute pancreatitis and tend to persist longer than the amylase elevations.[111] High lipase has been reported in a number of patients with cancer of the pancreas in whom the blood amylase was normal.[112] The lipase determination, incidentally, is of considerable significance in mumps. Strictly speaking, increased blood amylase, even in the presence of abdominal pain, cannot be interpreted as confirming the presence of pancreatitis in persons with mumps since this enzyme is contributed to the blood stream by the inflamed salivary gland; only lipase elevations are of diagnostic significance. Considerable confusion exists concerning the actual incidence of pancreatitis as a complication of mumps. Obvious clinical pancreatitis occurs in 2.4 per cent of the patients.[113] Elevations of blood amylase have been reported in 80 to 90 per cent but this, as stated, does not necessarily indicate pancreatitis.[114,115] Poppel and Bercow observed roentgen evidence of pancreatitis in 50 per cent of the patients examined by x-ray.[116] Lipase elevations have ranged between 12 per cent, which would suggest that the incidence of pancreatitis is relatively low in persons with mumps,[117] and 73 per cent; this leads to the conclusion that pancreatitis might be considered an integral manifestation of an infection of serozymogenic glands throughout the body.[118]

The serum lipase determination, although it appears to complement and extend the usefulness of the serum amylase test, has not gained widespread use. One reason for this is the complexity of the chemical estimation and the excessive length of analysis time, which varies from six to twelve hours depending upon the substrate used. Another factor is the lack of standardization for this procedure, which often fails to distinguish between the lipolytic activity of the serum due to esterase and that due to specific pancreatic lipase.[119]

Urinary enzyme levels: Elevation of the urinary amylase concentration has been used to diagnose acute pancreatitis.[120] Amylase is excreted by the kidney as a threshold substance. Thus elevations in blood amylase are reflected in the urine, although the appearance of rise in the latter may be delayed by the presence of renal insufficiency.[109] Although it has been claimed that elevation of urinary amylase levels may persist long after the disappearance of high concentrations in the blood,[120] many have found such wide variation in urinary amylase concentrations, even in the normal subject, that the value and reliability of these determinations have

been seriously questioned.[109] Danker and Heifetz have suggested that more significant data might be obtained if the urinary amylase were determined quantitatively in terms of rate of secretion rather than qualitatively.[109]

Although lipase levels in the urine had been studied in the past, little was done to apply these determinations as a diagnostic test until recently when Nothman reopened the subject and indicated such a possibility.[121,122] It was shown experimentally that lipase in the urine is of pancreatic origin, that it increases following administration of mecholyl® or secretin, and disappears following pancreatic resection.[121] In a clinical study of normal subjects, the lipase concentration and twenty-four hour content were found to change only slightly under varying conditions.[122] It is of interest to note that Nothman constructed his test of pancreatic function along the lines suggested by Danker and Heifetz[109] by studying the quantitative excretion of lipase in the urine after stimulation of the pancreas with secretin. In subjects with cancer of the pancreas and fibrotic pancreatitis, the urinary lipase response to secretin was less than that observed in normal subjects.

Provocative Blood Enzyme Tests: While unanimity of opinion exists regarding the value of blood enzyme determinations in acute pancreatitis, no such agreement exists concerning their diagnostic significance in chronic inflammation and cancer of the pancreas.[123] To be sure, there have been occasional reports of elevation of amylase and particularly of lipase in these conditions,[112,124] but the rarity of such findings precludes any diagnostic reliability.

The evanescence of enzyme elevation in acute disease of the pancreas and the lack of significance of such determinations in chronic pancreatitis and cancer of the pancreas have led to the development of provocative blood enzyme tests.[125] In these procedures serial determinations of the blood enzymes, amylase and/or lipase, are made preceding and following administration of drugs designed to (1) stimulate flow of pancreatic juice (secretin),[41,126–128] (2) stimulate production of pancreatic enzymes (doryl,®[123] mecholyl,[128] prostigmin®[129,130] and urecholine®[42]), and (3) obstruct the pancreatic duct system (morphine[127,131,132] and urecholine[42]). Depending upon the type of stimulus used, two patterns of response have been described,[128] (1) those in which the stimulus causes a rise in serum enzyme in normal subjects, the failure of which is then indicative of pancreatic insufficiency as seen in pancreatitis (these are the essential criteria when morphine is used alone), and (2) those in which the stimulus causes no elevation of enzyme in normal subjects but does in patients with obstructed pancreatic ducts such as occur in cancer of the pancreas (these are the essential criteria when secretin alone is used as a stimulus). The interpretation of results becomes more complex, of course, when a combination of drugs is administered.

The concept of the provocative tests is based upon the premise that in a gland in which there is no ductal obstruction stimulation neither of flow nor of ferment secretion will elevate the enzyme levels in the blood, whereas in the gland in which there is ductal obstruction either type of stimulation will result in a rise of enzyme in the blood to a level depending in large part upon the mass of functioning parenchyma. Thus two factors are always to be considered, the degree of ductal obstruction and the extent of parenchymal damage; these act in opposing directions in determining the degree of enzyme response to stimulation. Theoretically, therefore, it is not possible to construct criteria for a single test, although it might be possible to do so by combining the results obtained by using two different types of stimulant, the secretory and duct-obstructing, which would evaluate both factors.

Clinical experience has confirmed these hypotheses. Overlapping of data has been noted in most series and disparate findings have been reported by many observers.[123,125,128,133] In our own series of 192 patients studied with combinations of secretin, mecholyl, urecholine and morphine, the blood amylase responses could not be correlated with the known state of pancreatic function as determined by surgery and/or the secretin test.[125] The provocative tests remain biologic phenomena which, when giving positive results, should invite suspicion of disease of the pancreas but cannot be depended upon for diagnosis.

Blood Trypsin Levels and Blood Coagulation Tests: Trypsin levels in the blood serum have not been determined in the past because of the presence of potent enzyme inhibitors. Recent investigation, however, has shown that it is possible to separate trypsin from its inhibitors by chemical fractionation of the blood proteins. It seems probable that blood trypsin levels in patients with and without disease of the pancreas

will be reported in the near future. Until this is accomplished, the hypertrypsinemia presumed to exist in acute disease of the pancreas and the hypothetical alterations in blood trypsin levels in chronic disease of the pancreas and cancer of the pancreas can be recognized only by resultant changes in blood coagulability, proteolytic activity, and antiproteolytic, antifibrinolysin and/or antithrombin titers.[134]

These alterations in blood coagulation mechanisms have been long appreciated as fundamental manifestations of disease of the pancreas but only sporadic attempts had been made to utilize them in diagnosis until Innerfield and his associates aroused interest in this field by extensive reports indicating a potential significance of the plasma antithrombin titer.[135] This titer has been demonstrated experimentally to depend upon the rate of trypsin release into the bloodstream.[47]

Innerfield reported elevated antithrombin titers in patients with acute pancreatitis even after the blood amylase level had returned to normal.[136] High titers also were noted in the pressure of pancreatic cysts,[137] pancreatic tumors,[138] and in some cases of chronic pancreatitis;[135] low titers were observed in fibrocystic disease[139] and in advanced chronic pancreatic fibrosis.[135] Innerfield also claimed that antithrombin titers could be provocatively increased during remission in cases of chronic relapsing pancreatitis by the administration of prostigmin.[140]

The diagnostic value of the antithrombin titer has been confirmed by some in the diagnosis of acute pancreatitis[141] and fibrocystic disease.[142] Most investigators have not had such satisfactory results with the test.[143] In Dreiling's series of seventy-nine patients in whom the antithrombin titer was compared with the secretin test response, the blood amylase and the serum mucoprotein level in patients who had and in those who did not have disease of the pancreas, the antithrombin titer behaved much like the serum amylase.[144] It was often elevated in patients with acute pancreatitis in whom blood amylase was increased; occasionally it was elevated in such patients in whom the blood amylase had returned to normal levels. In patients with chronic pancreatitis and cancer of the pancreas, the antithrombin titer was observed to be low, normal or elevated. The weakness of the antithrombin test was found to be in the abnormal values, low or elevated, which were obtained in a significant percentage of subjects without disease of the pancreas.[144]

Shingleton et al.,[134] pursuing a line of investigation similar to that of the Innerfield group, developed the "Paritol C" blood coagulation test for disease of the pancreas. This test is based upon the premise that stimulation of the diseased pancreas results in hypertrypsinemia and that this in turn increases the blood coagulability, which effect can be estimated by titration against anticoagulant, heparin-like substances such as paritol C. Using prostigmin as the stimulant, Shingleton was able to produce a marked increase in blood coagulability, as evidenced by higher paritol C titers, in six of eleven patients who had cancer of the pancreas and in six of eight patients who had chronic pancreatitis. Similar results have been obtained by Moser et al.,[145] but it must be pointed out that the "Paritol" test and Nothman's proposed urinary lipase procedure are fundamentally provocative enzyme tests and, as such, subject to the same criticisms.

Abnormalities in Exocrine Secretory Capacity. Examination of duodenal drainage affords a direct means of assaying the external pancreatic secretion and also of disclosing the presence of cancer cells. In addition, corollary information concerning the function and patency of the biliary tract can be obtained. Although attempts have been made to study pancreatic function with mecholyl,[146,147] insulin hypoglycemia[148] and urecholine,[149] the most reliable stimulus is secretin.[150] The diagnostic value and reliability of the secretin test has been repeatedly confirmed.[151–156]

Secretin test: The secretin test is performed on patients in the fasting state. A double or bilumen gastroduodenal tube is so positioned fluoroscopically that with the use of gentle suction it is possible to obtain quantitative uncontaminated collection of gastric and duodenal juice. The standard stimulus is 1.0 clinical units of secretin, following which, samples are aspirated at intervals of sixty to eighty minutes. The duodenal drainage is examined for volume, bicarbonate concentration, enzyme content, guaiac reaction, biliary pigment concentration and cellular morphology. Of these, the first three factors characterize the pancreatic response to secretin.

In the normal patient, following the injection of secretin, a rapid increase occurs in pancreatic flow. Depending upon body size, 100 to 300 ml.

TABLE II

PANCREATIC AND BILIARY PIGMENT RESPONSE TO SECRETIN TEST
Differential Diagnostic Criteria

Diagnosis	Pancreatic Volume Response	Pancreatic Bicarbonate Response	Pancreatic Amylase Response	Biliary Pigment Response
Normal				
Adults	Average 3.2 ml./kg.	Average 108 mEq./L.	Average 14.2 u./kg.	.....
Infants	Average 0.8 ml./kg.	Average 58 mEq./L.	Average 59 u. (trypsin) *	.....
Children	Average 0.77 ml./kg.	Average 62 mEq./L.	Average 39 u. (trypsin) *	.....
Acute pancreatitis	Abnormal (or normal) †	Abnormal (or normal) †	Abnormal (or normal †)	Normal
Chronic pancreatitis	Normal (or abnormal) †	Abnormal	Normal (or abnormal) †	Normal
Fibrocystic disease	Abnormal	Abnormal	Abnormal	Abnormal
Pancreatic cancer				
Diffuse	Abnormal	Abnormal	Abnormal	Abnormal
Head	Abnormal	Abnormal (or normal) †	Abnormal (or normal) †	Abnormal
Body	Abnormal	Normal	Normal	Normal
Tail	Normal	Normal	Normal	Normal
Obstructive jaundice				
Papillary cancer	Abnormal	Normal (or abnormal) †	Normal (or abnormal) †	Abnormal
Biliary tract cancer	Normal	Normal	Normal	Abnormal
Biliary tract stone	Normal	Normal	Normal	Abnormal
Hepatitis	Normal	Normal	Normal	Normal
Sprue-celiac disease	Normal	Normal	Normal	Normal

* Trypsin figures are cited since amylase values are unreliable in infants and children.
† Less common response in parentheses.

may be obtained in an eighty minute collection. When there is obstruction to a main pancreatic duct or when the secreting parenchyma is destroyed by a pathologic process, a reduction of volume flow occurs. The bicarbonate concentration following administration of secretin rises and falls more slowly than the volume response. A maximum concentration as high as 140 mEq./L. may be obtained after twenty minutes. This maximum is markedly reduced in chronic inflammatory disease of the pancreas. The concentration of enzyme in pancreatic juice after secretin varies inversely with the rate of flow, the rate of enzyme secretion being unaltered. The enzyme concentration *per se* is not of great significance except under special circumstances, as in cystic fibrosis in which an all-or-none defect is usually present.[157] It is the total enzyme secretion which is of importance and which may be decreased in pancreatic duct obstruction and in parenchymal disease of the pancreas. In accordance with the concept of parallelism of enzyme secretion, it is convenient in most laboratories to determine only amylase. Gibbs[158] and others[157,159] have warned, however, that amylase secretion is unreliable as an index in infants and they have advocated the substitution of trypsin determinations in this group.

The range of norms can be established from a statistical study of the responses in normal subjects. These vary slightly depending upon the technic, the type of secretin used and the length of the collection period.[160] Since there is no evidence for the existence of hypersecretion of the external pancreatic gland as a clinical entity, only the lower limits of the normal range are of diagnostic import. These critical limits, derived by Dreiling[160] from a study of 172 normal subjects using secretin (Lilly) and a collection period of eighty minutes are (Table II): (1) for total volume, 2.0 ml. per kg. or more (average 3.2 ml. per kg.), (2) for maximum bicarbonate concentration, 90 mEq. per L. or more (average 108 mEq. per L.), and (3) for

total amylase secretion, 6.0 units per kg. or more (average 14.2 units per kg.). In infants and children Gibbs[158] has established other normal ranges. (Table II.)

Based upon clinical experience from 1,500 case studies, Dreiling[28] has described two abnormal secretin response types in patients with pancreatic disease: (1) A quantitative deficiency in which there is a tendency to reduction in volume with maintenance of bicarbonate and enzyme secretion. This is characteristic of pancreatic duct obstruction as seen in neoplasm. (2) A qualitative deficiency in which the volume secretion is sustained but the bicarbonate response and, to a lesser extent, the enzyme secretion is diminished. This type is indicative of chronic inflammatory disease of the pancreas.

The alteration of the secretin response in pancreatic tumor depends upon the degree and site of pancreatic duct obstruction.[161] (Table II.) The greatest abnormalities in volume reduction occur in the diffuse lesions and those involving the head of the pancreas, particularly the periampullary regions, because such lesions obstruct a major duct. Volume reduction is also encountered to a lesser extent in tumors of the neck and body, a fact of great diagnostic import because these malignancies in the early stages can hardly be recognized by any other means. They are suggested by a symptom complex of weight loss, diarrhea, diabetes and mid-back pain. Tumors of the tail of the pancreas produce no alteration in the secretin test because they obstruct no major duct nor do they involve a significant portion of the secretin tissue. Diabetes *per se* does not affect the external pancreatic secretion, nor do tumors contiguous to the pancreas.[161]

The secretin test has little practical value in the diagnosis of acute pancreatitis.[28] (Table II.) The functional capacity of the gland, paralleling the tissue repair, rapidly returns to the normal range during the first week of illness. In situations in which abnormal secretion is apt to be obtained, the patient is too ill for duodenal intubation; on the other hand, when the test is possible, normal drainage is likely to be observed. When the procedure is performed during the early acute phase, depressions in any or all of the three factors, volume, bicarbonate and amylase, may be encountered, attesting to the combined presence of ductal obstruction and extensive parenchymal damage. A normal test does not exclude acute pancreatitis. The rapidity with which the pancreatic secretion returns to normal in acute pancreatitis, although sharply limiting the diagnostic usefulness of the secretin test, enhances its prognostic value. Abnormal responses obtained several weeks after subsidence of all clinical signs and symptoms are indicative of persistent inflammation and the possibility of chronicity.[28]

In chronic pancreatitis, abnormal secretion is regularly encountered.[28] (Table II.) The characteristic defect is a marked depression of bicarbonate secretion.[29] Volume and enzyme secretion are spared in all but the most advanced cases. The prominence of the bicarbonate defect is due to the use of a specific stimulus which augments bicarbonate formation but does not affect enzyme elaboration.

The biliary pigment response in the secretin test depends upon the choleretic properties of the hormone and the patency of the biliary tract; it is a reflection of the flow of bile into the duodenum during the collection periods.[162,163] (Fig. 6.) If the function of the gallbladder is normal, bile disappears from the duodenal drainage during the test. In patients in whom the gallbladder does not function due to cholecystic disease or to cholecystectomy, high concentrations of bile persist throughout the test. Complete absence of bile, of course, points to biliary obstruction. Following cholecystectomy, incomplete common duct obstruction and dilatation may be diagnosed by the occurrence of a biliary pigment response indicating gallbladder capacity, which obviously is abnormal in the postcholecystectomy state.[164]

Correlation of the data of the pancreatic and biliary pigment responses to secretin are useful in the diagnosis of various gastrointestinal disorders. In obstructive jaundice, precise localization of the lesion is possible.[161] (Table II.) When there is evidence of both pancreatic and biliary tract obstruction, the lesion must be in the head of the pancreas. If pancreatic function is normal in the presence of biliary obstruction, the lesion is located in the extrahepatic biliary tract. Whenever pancreatic and biliary flow are normal in patients with jaundice, hepatocellular damage is indicated. Hepatitis *per se* does not alter pancreatic secretion but does affect the biliary pigment response. Thus the secretin test cannot be used to differentiate extrahepatic biliary obstruction from intrahepatic jaundice.[161]

In the postcholecystectomy syndrome, the secretin test is useful in disclosing the presence

of chronic pancreatitis and of ball-valve common duct stones.[164] It thus supplements intravenous cholangiography. Among patients with sprue, celiac disease, idiopathic steatorrheas, ulcerative colitis and ileitis, abnormal findings may demonstrate unsuspected pancreatic fibrosis which may have etiologic and therapeutic significance.[28] Study of patients who have migratory thrombophlebitis and thromboembolic phenomena will occasionally disclose that these patients have inflammatory disease of the pancreas or cancer of the pancreas.[165]

The secretin test has furnished significant data in elucidation of the proposed relationship between the pancreas and peptic ulceration. Although duodenal ulcer, even when penetrating the pancreas, does not produce clinically manifest pancreatitis[166] some suggestion has appeared that dysfunction of the pancreas may incite peptic ulceration. Thus duodenal, jejunal and marginal ulceration have been reported in association with islet tumor,[167–169] and deficient acid neutralization in the duodenum due to pancreatic insufficiency has been implicated in the etiology of primary peptic ulcer.[170] Moreover, several observers have postulated that postgastrectomy diarrheas are a result of deficient pancreatic flow.[171] However, secretin test studies in over seventy-five patients who have peptic ulcer and in fifteen patients who have postgastrectomy diarrhea and sprue syndrome have failed to disclose abnormalities of pancreatic secretion.

Finally, the duodenal juice obtained in the secretin test can be subjected to microscopic inspection for parasites and crystals and can be studied by cytologic technics for cancer cells. Lemon and Byrnes[172] and others[173,174] have reported a high incidence of smears which gave positive results for carcinoma cells in patients who had tumors of the pancreas. Such a procedure is of inestimable value in the difficult case in which the differential diagnosis lies between chronic pancreatitis and cancer of the pancreas.

REFERENCES

1. Thomas, J. E. The External Secretion of the Pancreas. Springfield, Ill., 1950. Charles C Thomas.
2. Bayliss, M. M. and Starling, E. H. The mechanism of pancreatic secretion. *J. Physiol.*, 28: 325, 1902.
3. Mellanby, J. The mechanism of pancreatic secretion—the function of secretin. *J. Physiol.*, 60: 85, 1925.
4. Harper, A. A. and Raper, H. S. Pancreozymin: stimulant of pancreatic enzymes in extracts of the small intestines. *J. Physiol.*, 102: 115, 1943.
5. Friedman, M. H. F. and Snape, W. J. Comparative effectiveness of extracts of the intestinal mucosa in stimulating the external secretions of the pancreas and liver. *Federation Proc.*, 4: 21, 1945.
6. Ivy, A. C. and Oldberg, E. A hormonal mechanism for gall bladder contraction and evacuation. *Am. J. Physiol.*, 86: 599, 1928.
7. Nasset, E. S. Enterocrinin, a hormone which excites the glands of the small intestine. *Am. J. Physiol.*, 121: 481, 1938.
8. Thomas, J. E. The effect of nervous and hormonal stimulation on zymogen secretion. *Federation Proc.*, 1: 261, 1942.
9. (*a*) Gayet, R. and Guillaumie, M. Sur les modifications de l'excrétion pancréatique consécutive a l'hypoglycemie des centres encephaliques. *Compt. rend. Soc. de biol.*, 105: 373, 1930; (*b*) Gayet, R. and Guillaumie, M. Les caracteres physiologiques de la secrétion pancréatique provoquée par la stimulation électrique du vagus. *Compt. rend. Soc. de biol.*, 111: 899, 1932.
10. Wang, C. C. and Grossman, M. I. Physiological determination of release of secretin and pancreozymin from intestine of dogs with transplanted pancreas. *Am. J. Physiol.*, 164: 527, 1951.
11. Anrep, G. V. The influence of the vagus on pancreatic secretion. *J. physiol.*, 50: 421, 1915.
12. Dreiling, D. A., Druckerman, L. J. and Hollander, F. The effect of complete vagisection and vagal stimulation on pancreatic secretion in man. *Gastroenterology*, 20: 578, 1952.
13. Shingleton, W. W., Blake, F. and Vetter, S. J. Pancreatic secretions and response to secretin after vagotomy and sympathectomy. *Federation Proc.*, 9: 315, 1950.
14. Pfeffer, R. B., Stephenson, H. E. and Hinton, J. W. The effect of thoracolumbar sympathectomy and vagus resection on pancreatic function. *Ann. Surg.*, 136: 585, 1952.
15. Baxter, S. G. Nervous control of the pancreatic secretion in the rabbit. *Am. J. Physiol.*, 96: 349, 1931.
16. Harper, A. A. and Vass, C. C. N. The control of the external secretion of the pancreas in cats. *J. Physiol.*, 99: 415, 1941.
17. Thomas, J. E. Physiology of the digestive tract. *M. Clin. North America*, 40: 273, 1956.
18. Kuntz, A. and Richins, C. A. The effects of direct and reflex nerve stimulation on the exocrine secretory activity of the pancreas. *J. Neurophysiol.*, 12: 29, 1949.
19. Dreiling, D. A. Effect of histamine and histalog on pancreatic secretion. *Gastroenterology*, 27: 334, 1954.
20. Dreiling, D. A., Richman, A. and Fradkin, N. F. The role of alcohol in the etiology of pancreatitis: a study of the effect of intravenous ethyl alcohol on the external secretion of the pancreas. *Gastroenterology*, 20: 636, 1952.
21. Thomas, J. E. and Crider, J. O. Carbohydrates as stimuli for the secretion of pancreatic enzymes. *Federation Proc.*, 6: 214, 1947.

22. Howat, H. T. and Schofield, B. The effect of urogastrone, enterogastrone, and mepyramine maleate on gastric and pancreatic secretion. *J. Physiol.*, 123: 1, 1954.
23. Pavlov, I. P. The Work of the Digestive Glands. London, 1902. C. Griffin & Co., Ltd.
24. Grossman, M. I. Gastrointestinal hormones. *Physiol. Rev.*, 30: 33, 1950.
25. Goldberg, R. C. and Chaikoff, I. L. Selective pancreatic acinar destruction with d, l-ethionine. *Arch. Path.*, 52: 230, 1951
26. Grossman, M. I. and Ivy, A. C. Effect of alloxan upon external secretion of the pancreas. *Proc. Soc. Exper. Biol. & Med.*, 63: 62, 1946.
27. Friedman, M. H. F. and Snape, W. J. Dissociation of secretion of pancreatic enzymes and bicarbonate in patients with chronic pancreatitis. *Gastroenterology*, 15: 296, 1950.
28. Dreiling, D. A. Studies in pancreatic function. v. The use of the secretin test in the diagnosis of pancreatitis and in the demonstration of pancreatic insufficiencies in gastrointestinal disorders. *Gastroenterology*, 24: 540, 1953.
29. Dreiling, D. A. and Janowitz, H. D. The secretion of electrolytes by the human pancreas. *Gastroenterology*, 30: 382, 1956.
30. Hart, W. H. and Thomas, J. E. Bicarbonate and chloride of pancreatic juice secreted in response to various stimuli. *Gastroenterology*, 4: 409, 1945.
31. Dreiling, D. A., Janowitz, H. D. and Halpern, M. The effect of a carbonic anhydrase inhibitor, diamox, on human pancreatic secretion. *Gastroenterology*, 29: 262, 1955.
32. Hollander, F. and Birnbaum, D. The role of carbonic anhydrase in pancreatic secretion. *Tr. New York Acad. Sc.*, 15: 56, 1952.
33. Véghelyi, P. V., Kemeny, T. T., Pozsonyi, J. and Sós, J. Dietary lesions of the pancreas. *Am. J. Dis. Child.*, 79: 658, 1950.
34. Grossman, M. I., Greengard, H. and Ivy, A. C. The effect of dietary composition on pancreatic enzymes. *Am. J. Physiol.*, 138: 676, 1943.
35. Farber, E. and Popper, H. Production of acute pancreatitis with ethionine and its prevention by methionine. *Proc. Soc. Exper. Biol. & Med.*, 74: 838, 1950.
36. Ågren, G. and Lagerlöf, H. The pancreatic secretion in man after intravenous administration of secretin. *Acta med. Scandinav.*, 90: 1, 1936.
37. Baxter, S. G. The parallel concentration of enzymes in pancreatic secretion. *Am. J. Digest. Dis.*, 2: 108, 1935.
38. Janowitz, H. D. and Hollander, F. The exocrine-endocrine partition of enzymes in the digestive tract. *Gastroenterology*, 17: 591, 1951.
39. Levy, A. H. and Levine, S. Uropepsin excretion in clinical surgery. *Gastroenterology*, 30: 270, 1956.
40. (*a*) Grossman, M. I. Experimental pancreatitis. *Arch. Int. Med.*, 96: 298, 1955; (*b*) Powers, S. R., Jr., Brown, H. H. and Stein, A. The pathogenesis of acute and chronic pancreatitis. *Ann. Surg.*, 142: 690, 1955.
41. Lopøusniak, M. S. and Bockus, H. L. Study of pancreatic serum enzymes following secretin injections in pancreatic affections. *Gastroenterology*, 16: 294, 1950.
42. Wirts, C. W. and Snape, W. J. Evaluation of pancreatic function tests. *J. A. M. A.*, 145: 876, 1951.
43. Gibbs, G. E. and Ivy, A. C. Early histologic changes following obstruction of pancreatic ducts in dogs: correlation with serum amylase. *Proc. Soc. Exper. Biol. & Med.*, 77: 251, 1951.
44. Howell, C. W. and Bergh, G. S. Pancreatic duct filling during cholangiography: its effect upon serum amylase levels. *Gastroenterology*, 16: 309, 1950.
45. Wapshaw, H. The pancreatic side effects of morphine. *Brit. J. Med.*, 1: 373, 1953.
46. Rush, B. and Clifton, E. E. The role of trypsin in the pathogenesis of acute hemorrhagic pancreatitis and the effect of an antitryptic agent in treatment. *Surgery*, 31: 349, 1952.
47. Innerfield, I., Schwarz, A. and Angrist, A. Intravenous trypsin: its anticoagulant, fibrinolytic, and thrombolytic effects. *J. Clin. Investigation*, 31: 1049, 1952.
48. Storer, J. and Kazdan, P. The relationship of the pancreas to blood coagulation. *Surgery*, 33: 683, 1953.
49. Lasher, E. P. and McCabe, M. M. Changes in coagulation time associated with experimental pancreatitis. *Arch. Surg.*, 60: 164, 1950.
50. Shinowara, G. Y., Waite, J. H. and Saleeby, R. G. Plasma coagulation factors in acute pancreatitis. *Proc. Soc. Exper. Biol. & Med.*, 83: 423, 1953.
51. Innerfield, I., Angrist, A. and Benjamin, J. W. Studies in trypsin: i. The anticoagulant action of trypsin. *Gastroenterology*, 20: 630, 1952.
52. Innerfield, I., Angrist, A. A. and Schwarz, A. Parenteral administration of trypsin, clinical effects in 538 patients. *J. A. M. A.*, 152: 197, 1953.
53. Opie, E. L. The relationship of cholelithiasis to disease of the pancreas to fat necrosis. *Am. J. M. Sc.*, 121: 27, 1901.
54. Sterling, J. A. The Biliary Tract. Baltimore, 1955. Williams & Wilkins Co.
55. Lueth, H. C. Studies on the flow of bile into the duodenum and the existence of a sphincter of Oddi. *Am. J. Physiol.*, 99: 237, 1931.
56. Shingleton, W. W., Anylan, W. G. and Hart, D. Effects of vagotomy, splanchnicectomy, and celiac ganglionectomy on experimentally produced spasm of the sphincter of Oddi in animals. *Ann. Surg.*, 135: 721, 1952
57. Bergh, G. S. Effect of food upon the sphincter of Oddi in human subjects. *Am. J. Digest. Dis.*, 9: 40, 1942.
58. Ryan, J. D., Doubilet, H. and Mulholland, J. H. Observations on biliary-pancreatic dynamics in a normal human. *Gastroenterology*, 13: 1, 1949.
59. Nossel, H L The effect of morphine on the serum and urinary amylase and the sphincter of Oddi: with some preliminary observations on the effect of alcohol on the serum amylase and the sphincter of Oddi. *Gastroenterology*, 29: 409, 1955.
60. Butsch, W. L., McGowan, J. M. and Walters, W. Clinical studies on the influence of certain drugs in relation to biliary pain and to the variations in

intrabiliary pressure. *Surg., Gynec. & Obst.*, 63: 451, 1936.

61. Menguy, R. B., Bellman, J. L., Grindlay, J. H. and Cain, J. B. Biliary stasis produced by chlorpromazine: an experimental study. *Proc. Staff Meet., Mayo Clin.*, 30: 601, 1955.
62. Mann, F. C. and Giordano, A. S. The bile factor in pancreatitis. *Arch. Surg.*, 6: 1, 1923.
63. Cameron, A. L. and Noble, J. F. Reflux of bile up the duct of wirsung caused by an impacted biliary calculus. *J. A. M. A.*, 82: 1410, 1924.
64. Howard, J. and Jones, R. The anatomy of the pancreatic ducts: the etiology of acute pancreatitis. *Am. J. M. Sc.*, 214: 617, 1947.
65. Sterling, J. A. The common channel for bile and pancreatic ducts. *Surg., Gynec. & Obst.*, 98: 420, 1954.
66. Kleitsch, W. P. Anatomy of the pancreas: a study with special reference to the duct system. *Arch. Surg.*, 71: 795, 1955.
67. Harms, E. Über Druckmessungen in Gallen- und Pankreasgangssystem. *Arch. f. klin. chir.*, 147: 637, 1927.
68. Rich, A. R. and Duff, G. L. Experimental and pathological studies on the pathogenesis of acute hemorrhagic pancreatitis. *Bull. Johns Hopkins Hosp.*, 58: 212, 1936.
69. Parry, E. W., Hallenbeck, G. A. and Grindlay, J. H. Pressures in the pancreatic and common ducts; values during fasting, after various meals, and after sphincterotomy: an experimental study. *Arch. Surg.*, 70: 757, 1955.
70. Wulsin, J. H. and Siler, V. E. The intraductal secretory pressures of the pancreas in unanaesthetized dogs. *Surgery*, 34: 9, 1953.
71. Waldron, J. M. Amylase activity of canine pancreatic juice. *Am. J. Physiol.*, 168: 283, 1952.
72. Kunitz, M. and Northrup, J. H. Crystalline chymo-trypsin and chymo-trypsinogen: I. Isolation, crystallization, and general properties of a new proteolytic enzyme and its precursor. *J. Gen. Physiol.*, 18: 433, 1935.
73. Grossberg, A. L., Komarov, S. A. and Shay, H. Distribution of proteins and enzymatic activities in electrophoretic components of canine pancreatic juice. *Am. J. Physiol.*, 168: 269, 1952.
74. Ziffrin, S. E. and Hosie, R. T. Pancreatic collagenase. *Proc. Central Soc. Clin. Research*, 28: 86, 1955.
75. Kalser, M. H. and Grossman, M. I. Secretion of trypsin inhibitor in pancreatic juice. *Gastroenterology*, 29: 35, 1955.
76. Kalser, M. H. and Grossman, M. I. Pancreatic secretion in dogs with ethionine-induced pancreatitis. *Gastroenterology*, 26: 189, 1954.
77. Troll, W. and Doubilet, H. The determination of proteolytic enzymes and proenzymes in human pancreatic juice. *Gastroenterology*, 19: 326, 1951.
78. Whitfield, A. G. W., Gourevitch, A. and Thomas, G. Metabolic effects of total pancreatectomy in man. *Lancet*, 1: 180, 1952.
79. Dragstadt, L. R., Clarke, J. S., Hlavacek, G. R. and Harper, P. V., Jr. Relation of the pancreas to the regulation of the blood lipids. *Am. J. Physiol.*, 179: 439, 1954.
80. Pratt, J. H. A study of steatorrhea with special reference to its occurrence in pancreatic disease and sprue. *Am. J. M. Sc.*, 187: 222, 1934.
81. Andersen, D. H. Celiac syndrome: determination of fat in feces. Reliability of two chemical methods and of microscopic estimate; excretion of fat and fecal fat in normal children. *Am. J. Dis. Child.*, 69: 141, 1945.
82. Holt, L. E., Jr. Celiac disease: what is it? *J. Pediat.*, 46: 369, 1955.
83. Dreiling, D. A. An evaluation of pancreatic function tests. *New York State J. Med.*, 53: 671, 1953.
84. Thaysen, T. E. H. Pancreatogenous fatty diarrhea. Report of a case. *Arch. Int. Med.*, 42: 352, 1928.
85. Johnstone, D. E. Studies in cystic fibrosis of the pancreas. Role of various diluents and the dilution factor in the interpretation of the x-ray film test for fecal trypsin. *Am. J. Dis. Child.*, 84: 191, 1951.
86. West, C. D., Wilson, J. L. and Eyles, R. Blood amino nitrogen levels: changes in the blood amino nitrogen levels following ingestion of proteins and of a protein hydrolysate in infants with normal and deficient pancreatic function. *Am. J. Dis. Child.*, 72: 251, 1946.
87. Anfanger, H. and Heavenrich, R. M. Amino acid tolerance tests in children. *Am. J. Dis. Child.*, 77: 425, 1949.
88. Althausen, T. L. and Uyeyama, K. A new test of pancreatic function based on starch tolerance. *Ann. Int. Med.*, 41: 563, 1954.
89. Kalser, M. H. Comparison of the glucose and starch tolerances, the secretin test, and fecal balance studies in patients with pancreatic disease. Panamerican Congress of Gastroenterology, Havana, Cuba, 1956.
90. Chinn, A. B., Lavik, P. S., Stitt, R. M. and Buckaloo, G. W. Use of I^{131}-labelled protein in the diagnosis of pancreatic insufficiency. *New England J. Med.*, 247: 877, 1952.
91. Lavik, P. S., Matthews, L. W., Buckaloo, G. W., Lemm, F. J., Spector, S. and Friedell, H. L. Use of I^{131}-labelled protein in the study of protein digestion and absorption in children with and without cystic fibrosis of the pancreas. *Pediatrics*, 10: 667, 1952.
92. Shingleton, W. W., Wells, M. H., Baylin, G. J., Ruffin, J. M. and Saunders, A. The use of radioactive labeled protein and fat in the evaluation of pancreatic disorders. *Surgery*, 38: 134, 1955.
93. Adlersberg, D. and Sobotka, H. Fat and vitamin A absorption in sprue and jejunoileitis. *Gastroenterology*, 1: 357, 1943.
94. Silverman, F. N. and Shirkey, H. C. A fat absorption test using iodinized oil with particular application as a screening test in the diagnosis of fibrocystic disease of the pancreas. *Pediatrics*, 15: 143, 1955.
95. Nardi, G. L. Phospholipid synthesis in patients with pancreatic disease. *Arch. Surg.*, 69: 726, 1954.
96. Popper, H. L. and Necheles, H. Pathways of enzymes into the blood in acute damage of the pancreas. *Proc. Soc. Exper. Biol. & Med.*, 43: 220, 1940.

97. Cope, O., Kapnick, I., Lambert, A., Pratt, T. D. and Verlot, M. G. Endocrine function and amylase activity. II. Changes in activity of blood serum amylase in response to changes in adrenal cortical function in the dog and rabbit. *Endocrinology*, 25: 236, 1939.
98. Howard, J. M., Frawley, J. P. and Artz, C. P. A study of plasma amylase activity in the combat casualty: the systemic response to injury. *Ann. Surg.*, 141: 337, 1955.
99. Cummins, A. J. and Bockus, H. L. Abnormal serum pancreatic enzyme values in liver disease. *Gastroenterology*, 18: 518, 1951.
100. Machella, T. E. Useful diagnostic laboratory procedures in pancreatitis. *Arch. Int. Med.*, 96: 322, 1955.
101. Howard, J. M., Smith, A. K. and Peters, J. J. Acute pancreatitis: pathways of enzymes into the blood stream. *Surgery*, 26: 161, 1949.
102. Popper, H. L. and Plotke, F. Studies on pancreatitis: observations on the disappearance of experimentally increased blood amylase and lipase. *Surgery*, 9: 706, 1941.
103. Raffensperger, E. C. Elevated serum pancreatic enzyme values without intrinsic pancreatic disease. *Ann. Int. Med.*, 35: 342, 1951.
104. Lewisohn, E. F. The clinical value of the serum amylase test. *Surg., Gynec. & Obst.*, 72: 202, 1941.
105. Smith, J. L., Walters, R. L. and Beal, J. M. A study of choledochal sphincter action. *Gastroenterology*, 20: 129, 1952.
106. Mahaffey, J. H., Brockman, H. L., Jordan, G. L. and Howard, J. M. A study of the serum amylase concentration in patients with acute perforation of gastroduodenal ulcers. *Surg., Gynec. & Obst.*, 101: 129, 1955.
107. Dozzi, D. L. Origin of blood amylase and blood lipase in the dog. Relation between blood and urinary amylase following induction of uranium nephritis. *Arch. Int. Med.*, 68: 232, 1941.
108. Bogoch, A., Roth, J. L. A. and Bockus, H. L. The effects of morphine on serum amylase and lipase. *Gastroenterology*, 26: 697, 1954.
109. Danker, A. and Heifetz, C. J. The interrelationship of blood and urinary diastase during transient acute pancreatitis. *Gastroenterology*, 18: 207, 1951.
110. Pfeffer, R. B., Stephenson, H. E., Jr. and Hinton, J. W. The effect of morphine, demerol and codeine on serum amylase values in man. *Gastroenterology*, 23: 482, 1953.
111. Comfort, M. W. and Osterberg, A. E. Serum amylase and serum lipase in the diagnosis of disease of the pancreas. *M. Clin. North America*, 24: 1137, 1940.
112. Johnson, T. A. and Bockus, H. L. The present status of the serum lipase test. *Am. J. Digest Dis.*, 10: 1, 1943.
113. Bradhy, M. B. and Sheffer, I. H. Pancreatitis complicating mumps. *Am. J. M. Sc.*, 181: 255, 1931.
114. Applebaum, I. L. Serum amylase in mumps. *Ann. Int. Med.*, 21: 35, 1944.
115. Bass, L. and Tudor, R. B. Serum amylase levels in mumps. *Journal-Lancet*, 69: 188, 1949.
116. Poppel, M. H. and Bercow, C. The roentgen manifestations of pancreatitis complicating mumps. *Am. J. Roentgenol.*, 61: 219, 1949.
117. Candel, S. and Wheelock, M. C. Serum amylase and serum lipase in mumps. *Ann. Int. Med.*, 25: 88, 1946.
118. Warren, W. R. Serum amylase and lipase in mumps. *Am. J. M. Sc.*, 230: 161, 1955.
119. Komarov, S., Shay, H. and Zislin, C. Lipolytic activity of human blood serum: method for its determination and its possible relation to pancreatic lipase. *Federation Proc.*, 12: 80, 1953.
120. Dozzi, D. L. Urinary amylase: its estimation and significance. *Am. J. Digest. Dis.*, 7: 123, 1940.
121. Nothman, M. M., Pratt, J. H. and Callow, A. D. Studies on urinary lipase. I. On a fat splitting enzyme in urine and its relation to pancreas. *Arch. Int. Med.*, 95: 224, 1955.
122. Nothman, M. M., Pratt, J. H. and Callow, A. D. Studies on urinary lipase. III. Urinary lipase in man. *Arch. Int. Med.*, 96: 188, 1955.
123. Royer, M., Noir, A. and Fernandez, D. E. Valor de las curvas de lipasemia y amilasemia producidas por la carbaminolcolina, en el estudio de los procesos pancreaticos chronicos. *Prensa méd. argent.*, 39: 2833, 1952.
124. Gambill, E. E., Waugh, J. M. and Dockerty, M. B. Persistent elevation of serum amylase and lipase due to carcinoma of the pancreas masquerading as chronic pancreatitis: report of case. *Gastroenterology*, 17: 290, 1951.
125. Dreiling, D. A. and Richman, A. Evaluation of provocative blood enzyme tests employed in the diagnosis of pancreatic disease. *Arch. Int. Med.*, 94: 197, 1954.
126. Myhre, J., Nesbitt, S. and Hurley, J. T. Response of serum amylase and lipase to pancreatic stimulation as a test of pancreatic function. *Gastroenterology*, 13: 127, 1949.
127. Snape, W. J., Wirts, C. W. and Friedman, M. H. F. Evaluation of pancreatic function by means of induced hyper-amylasemia following morphine and secretin. *Am. J. Med.*, 7: 417, 1949.
128. Sachar, L. A., Probstein, J. G. and Whittico, J. M. The effect of pancreatic stimulants on blood diastase. *Gastroenterology*, 18: 104, 1951.
129. Knight, W. A., Muether, R. O. and Sommer, A. J. Chronic recurring pancreatitis: serial serum diastase levels following prostigmine stimulation. *Gastroenterology*, 12: 34, 1949.
130. Malinkowski, T. S. Serum amylase response to pancreatic stimulation as a test of pancreatic disease. *Am. J. M. Sc.*, 222: 440, 1951.
131. Lagerlöf, H. Normal esterases and pancreatic lipase in blood. Study with new chemical and clinical methods (second secretin test). *Acta med. Scandinav.*, 120: 407, 1945.
132. Burke, J. O., Plummer, K. and Bradford, S. Serum amylase response to morphine, mecholyl, and secretin as a test of pancreatic function. *Gastroenterology*, 15: 699, 1950.
133. Heffernon, E. W. and Gunter, A. R. Evaluation of the secretin test in pancreatic disease. *Gastroenterology*, 19: 526, 1951.
134. Shingleton, W. W., Anlyan, W. G. and Hart, D. The diagnosis of pancreatic disorders by certain

laboratory procedures. *Ann. Surg.*, 136: 578, 1952.

135. Innerfield, I., Angrist, A. and Benjamin, J. W. Plasma antithrombin patterns in disturbances of the pancreas. *Gastroenterology*, 19: 843, 1946.
136. Innerfield, I., Angrist, A. and Benjamin, J. W. Antithrombin titre in acute pancreatitis. *Am. J. Med.*, 12: 24, 1952.
137. Innerfield, I., Angrist, A. and Benjamin, J. W. The antithrombin titre in pancreatic cyst. *Am. J. Surg.*, 83: 538, 1952.
138. Innerfield I. and Angrist, A. The plasma antithrombin determination: a new test for cancer of the pancreas associated with jaundice. *Am. J. M. Sc.*, 223: 422, 1952.
139. Innerfield, I., Angrist, A. and Benjamin, J. W. The antithrombin titer in cystic fibrosis of the pancreas: a preliminary report. *J. Pediat.*, 39: 287, 1951.
140. Innerfield, I. Acute pancreatitis: the antithrombin titre as an aid in diagnosis and prognosis. *New York State J. Med.*, 52: 2239, 1952.
141. Mosely, V., Seymour, W. and Pappas, A. Some observations on the plasma antithrombin test as a diagnostic aid. *South. M. J.*, 47: 476, 1954.
142. MacFarlane, J. C. W. Serum-antithrombin level in fibrocystic disease to the pancreas. *Lancet*, 263: 311, 1952.
143. Berk, J. E. Diagnostic features of pancreatic disease. *J. A. M. A.*, 159: 1079, 1955.
144. Dreiling, D. A., Greenspan, E. M. and Sanders, M. A correlative-study of the external pancreatic secretion, the plasma antithrombin titer, the blood amylase concentration, and the serum mucoprotein level in patients with and without pancreatic disease. *Gastroenterology*, 27: 755, 1954.
145. Moser, R. H., Rosenak, B. D. and Pierce, W. J. A test for coagulability of the blood in carcinoma of the pancreas. Am. Gastroenterol. Association Annual Meeting, San Francisco, 1954.
146. Bauman, L. Diagnosis of Pancreatic Disease. Philadelphia, 1949. J. B. Lippincott Co.
147. Comfort, M. W. and Osterberg, A. E. Pancreatic secretion in man after stimulation with secretin and acetylbetamethylcholine chloride. A comparative study. *Arch. Int. Med.*, 66: 688, 1940.
148. Diamond, J. S. and Siegal, S. A. The secretin test in the diagnosis of pancreatic disease with a report of one hundred and thirty tests. *Am. J. Digest. Dis.*, 7: 435, 1940.
149. Kyle, G. C., Machella, T. E., Lorber, S. H., Hilsman, J. T., Reinhold, J. G. and Brown, J. C. The use of urecholine as a stimulant of the external secretion of pancreas. *Gastroenterology*, 16: 285, 1950.
150. Ågren, G., Lagerlöf, H. and Berglund, H. The secretin test of pancreatic function in the diagnosis of pancreatic disease. *Acta med. Scandinav.*, 90: 224, 1936.
151. Diamond, J. S., Siegal, S. A., Gall, M. B. and Karlen, S. The use of secretin as a clinical test of pancreatic function. *Am. J. Digest. Dis.*, 6: 366, 1939.
152. Pollard, H. L., Miller, L. and Brewer, W. A. A clinical study of the secretin test. *Am. J. Digest. Dis.*, 9: 68, 1942.
153. Friedman, M. H. F. and Snape, W. J. Pancreatic secretion in man in response to administration of secretin and insulin. *Federation Proc.*, 6: 107, 1947.
154. Lake, M. Diagnostic value of the secretin test, including a report of nineteen operated or autopsied cases with anatomical studies of the pancreas. *Am. J. Med.*, 3: 18, 1947.
155. Dreiling, D. A. and Hollander, F. Studies in pancreatic function. I. Preliminary series of clinical studies with the secretin test. *Gastroenterology*, 11: 714, 1948.
156. Doubilet, H. Value of the secretin test in surgery. *S. Clin. North America*, 29: 489, 1949.
157. Andersen, D. H. Pancreatic enzymes in the duodenal juice in the celiac syndrome. *Am. J. Dis. Child.*, 63: 643, 1942.
158. Gibbs, G. E. Secretin test with bilumen gastroduodenal drainage in infants and children. *Pediatrics*, 5: 941, 1950.
159. Maddock, C. L., Farber, S. and Shwachman, H. Pancreatic function and disease in early life. II. Effect of secretin on pancreatic function of infants and children. *Am. J. Dis. Child.*, 66: 370, 1943.
160. Dreiling, D. A. and Hollander, F. Studies in pancreatic function II. A statistical study of pancreatic secretion following secretin in patients without pancreatic disease. *Gastroenterology*, 15: 620, 1950.
161. Dreiling, D. A. Studies in pancreatic function. IV. The use of the secretin test in the diagnosis of tumors in and about the pancreas. *Gastroenterology*, 18: 184, 1951.
162. Snape, W. J., Friedman, M. H. F. and Swenson, P. C. Correlation between the cystogram and the secretin test for gall bladder function. *Am. J. M. Sc.*, 216: 188, 1948.
163. Dreiling, D. A. and Lipsay, J. J. The use of the secretin test in the diagnosis of biliary tract disease. A report of 327 cases. *Gastroenterology*, 17: 242, 1951.
164. Dreiling, D. A. Studies in pancreatic function. III. The use of the secretin test in the diagnosis of patients with the post-cholecystectomy syndrome. *Gastroenterology*, 16: 162, 1950.
165. Dreiling, D. A., Blum, L. and Sanders, M. Thrombophlebitis, blood coagulation and pancreatic disease. A study of the pancreatic secretion in patients with thrombophlebitis. *Arch. Int. Med.*, 96: 490, 1955.
166. Caruolo, J. E., Hallenbeck, C. A. and Dockerty, M. B. A clinicopathologic study of posterior penetrating gastric ulcers. *Surg., Gynec. & Obst.*, 101: 759, 1955.
167. Janowitz, H. D. and Crohn, B. B. Hyperinsulinism and duodenal ulcer. A rare clinical condition. *Gastroenterology*, 17: 578, 1951.
168. Forty, F. and Barret, G. M. Peptic ulceration of the third part of the duodenum associated with islet cell tumors of the pancreas. *Brit. J. Surg.*, 40: 60, 1952.
169. Zollinger, R. M. and Ellison, E. H. Primary peptic ulceration of the jejunum associated with islet cell tumor of the pancreas. *Ann. Surg.*, 142: 709, 1955.

170. Poth, E. J. and Fromm, S. M. The relation of pancreatic secretion to peptic ulcer formation. *South. Med.*, 33: 16, 1952.
171. Everson, T. C. Collective review: nutrition following total gastrectomy with particular reference to fat and protein assimilation. *Internat. Abstr. Surg.*, 95: 209, 1952.
172. Lemon, H. M. and Byrnes, W. W. Cancer of the biliary tract and pancreas: diagnosis from cytology of duodenal aspiration. *J. A. M. A.*, 141: 254, 1949.
173. McNeer, G. and Ewing, J. H. Exfoliated pancreatic cancer cells in duodenal drainage: a case report. *Cancer*, 2: 643, 1949.
174. Rubin, C. E., Massey, B. W., Kirsner, J. B., Palmer, W. L. and Stonecypher, D. D. The clinical value of gastrointestinal cytology. *Gastroenterology*, 25: 119, 1953.

Clinico-pathologic Conference

Secondary Hyperparathyroidism

STENOGRAPHIC reports, edited by Amoz I. Chernoff, M.D. and W. Stanley Hartroft, M.D. of weekly clinico-pathologic conferences held in the Barnes and Wohl Hospitals, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, a forty-two year old housewife (No. 09065), was admitted to Barnes Hospital for the first time in 1946 and died during her second admission on October 22, 1955. Her chief complaints at the time of the second admission were joint pains of three to four years' duration and painful blue blotches on her legs of six months' duration.

In 1935, during the third trimester of her first pregnancy, she had proteinuria, elevated blood pressure and slight ankle edema without other complaints. Following delivery of a normal infant, these manifestations disappeared. The patient remained asymptomatic for three years when the same sequence of events took place in the third trimester of her second pregnancy. On this occasion she also noted periorbital edema on awakening. Again she became asymptomatic following delivery. The patient was not examined between these two pregnancies. In 1942, during the last trimester of a third pregnancy, she again had proteinuria, hypertension, weight gain, mild headaches and shortness of breath. Labor was induced at term, using castor oil and quinine, and a stillborn infant was delivered. There were no postpartum complications, and the patient was asymptomatic following delivery. A year later a fourth pregnancy ended in abortion during the first trimester. In 1945 her fifth pregnancy was terminated during the second month because of increasing hypertension, proteinuria, ankle edema and headaches. The proteinuria, hypertension and headaches persisted, however. Six months later the patient noticed swelling of her face, hands, feet and legs. She had no sore throats, but her family physician made a diagnosis of tonsillitis and tonsillectomy was performed. She was told that her systolic blood pressure was 170 at that time. Because of the persistence of edema she was admitted to Barnes Hospital (1946).

On admission her blood pressure was 155/105. The pulse, respirations and temperature were normal. She appeared well developed and well nourished. There was slight pretibial, sacral and periorbital edema. The fundi were described as being normal. The heart was not enlarged, and a grade 2 to 3 harsh systolic murmur was heard both at the base and at the apex. The remainder of the physical examination was normal. Hemoglobin was 11.4 gm. per cent, red blood cell count, 3.85 million per cu. mm., white blood count 9,600 per cu. mm., differential count: eosinophils 3, segmented forms 41, lymphocytes 53, monocytes 3. Red blood cells appeared slightly hypochromic and platelets were adequate. Urinalysis revealed numerous white blood cells, red blood cells and occasional granular casts as well as 4+ proteinuria. Nonprotein nitrogen was 21 mg. per cent. Total serum protein was 3.4 gm. per cent of which 1.9 gm. was albumin and 1.5 gm. globulin. A concentration diuresis test revealed a urinary specific gravity ranging from 1.015 to 1.003. A twenty-four-hour quantitative urinary protein was 3.1 gm. Serum phosphorus was 5.1 mg. per cent and hepatic function tests were normal. An electrocardiogram was normal as was a roentgenogram of the chest. Intravenous pyelograms revealed no abnormality except for osteitis condensans ilii. A diagnosis of chronic glomerulonephritis, nephrotic stage, was made and the patient was discharged with instructions to eat a high protein, low salt diet.

She continued to be edematous for the next three years, at the end of which she noted moderate polyuria and nocturia; edema disappeared. In 1949 the patient had an episode of severe menorrhagia and required three blood transfusions. She was then treated with "liver and iron" which she continued to take until admission. In 1950 she again had menorrhagia

and received three blood transfusions. Except for these episodes of menorrhagia the patient was asymptomatic and was able to carry out her household duties. In 1951 she was permitted to take a normal diet without salt restriction and the edema did not reappear. The following year the patient began to have severe pains in her knees, hips, elbows and shoulders, and also had a stiff back. The pains became progressively more severe particularly in the legs and a year prior to her final admission she began to use crutches. During the last six months of this period the pain was so severe that she was confined to her bed and chair. During the time that she had severe joint pains (three to four years), she also noted increased frequency of urination with nocturia of three to six times per night. One year prior to the final admission slight tenderness developed in the epigastrium and the patient's family doctor made a clinical diagnosis of peptic ulcer. She was treated with antacids and a soft diet, with relief of symptoms. About this time she began noticing that the ends of her fingers were swollen and that her thumb nails were curved downward. She also had occasional pain and numbness of her fingertips. During the year prior to admission the patient received nine blood transfusions because of anemia, the last transfusion being in September, 1955. Six months prior to the final admission she began to lose weight totaling about 30 pounds. Also, painful "blue blotches" began to develop on her legs and a few on her arms. These gradually increased in size and number and tended to become confluent. Two months later the patient became anorexic and ate very little. Shortly thereafter she began having all of her remaining twenty-five teeth removed; the extractions were completed one month before entry to the hospital. She noted no difficulty with bleeding. One week prior to admission she was treated with prednisone and digitalis. While on this regimen severe nausea and vomiting developed which persisted until hospital admission.

During childhood the patient had had one episode of inflammatory rheumatism involving the left hip. In 1943 she had had mild jaundice associated with nausea and vomiting for two weeks.

Physical examination on October 22, 1955, revealed the temperature to be 36.5°C.; pulse 114 and regular; respirations 16; blood pressure 210/120. The patient was a chronically ill, malnourished woman who looked twenty years older than her stated age; she had pasty sallow skin, uriniferous breath and no teeth. There were many confluent ecchymotic areas on both the upper and lower extremities, most marked on the legs. No lymph nodes were felt. Examination of the fundi revealed marked narrowing of the arterioles and some old resolving hemorrhages. Examination of the ears, nose and throat was unremarkable. Her neck was supple. The thyroid was not felt and the veins were not distended. The lungs were clear to percussion and auscultation. The point of maximum impulse was in the fifth intercostal space at the mid-clavicular line. A_2 was greater than P_2. There was a grade 3 harsh, apical systolic murmur transmitted to the precordium. The abdomen was soft. The liver, felt 2 cm. below the right costal margin, was firm and slightly tender. The spleen was not felt. The lower poles of both kidneys were questionably palpable. Examination of the extremities revealed an eschar on the right lower calf laterally 2 by 3 cm. in diameter and quite tender. There was mild tenderness of the calves and erythema and early clubbing of all fingers. The radial and femoral pulses were barely palpable. All of the peripheral arteries were described as being beady and non-compressible. Similar blood vessels were also palpable on the anterior chest wall. The neurologic examination was normal except for generalized muscular wasting and weakness.

Laboratory data were as follows: red blood cell count, 3.5 million per cu. mm.; hemoglobin, 10.7 gm. per cent; white blood cell count, 18,600 per cu. mm.; differential count: eosinophils 1, segmented forms 84, lymphocytes 12, monocytes 3. Platelets appeared adequate. Red blood cells were normocytic and normochromic. Urinalysis revealed a specific gravity of 1.011; reaction, 5.0; protein, 4+; sugar, negative; Sulkowitch, 2+; microscopic 10 to 12 white blood cells and 5 to 6 red blood cells per high power field. Stool examination was guaiac-negative. Blood cardiolipin reaction was negative. Blood chemical determinations were as follows: non-protein nitrogen, 347 mg. per cent; sodium, 136.7 mEq./L.; potassium, 4.9 mEq./L.; chloride, 95 mEq./L.; CO_2, 12.8 mEq./L.; total serum protein, 5.3 gm. per cent; albumin, 3.4 gm. per cent; globulin, 1.9 gm. per cent; cholesterol, 256 mg. per cent; uric acid, 12 mg. per cent; serum calcium, 11.5 mg. per cent; serum phosphorus, 17.3 mg. per cent; alkaline phosphatase, 9.3 Bodansky units; prothrombin

time, 60 per cent of normal. An electrocardiogram was interpreted as showing sinus tachycardia, left ventricular enlargement and question of an old diaphragmatic myocardial infarction. An LE preparation was negative. The bleeding time, clotting time and platelet count were within normal limits. A roentgenogram of the chest was interpreted as showing multiple subcutaneous calcifications and sclerosis of the bones of the dorsal spine, proximal humeri and scapulas. Cardiac enlargement, chiefly left ventricular was noted. Roentgenograms of the abdomen, left hip and shoulder were interpreted by the radiologist as showing changes compatible with nephrosclerosis, arterial calcification, secondary hyperparathyroidism with osteitis fibrosa cystica generalisata, and an acute type of bone atrophy secondary to hyperparathyroidism.

The patient was kept at bedrest and given a low protein diet. Chloral hydrate was used for sedation and chlorpromazine was used to control nausea and vomiting. For the most part blood pressure ranged between 200/140 to 160/100 with occasional readings of 130/80. The patient was afebrile throughout her hospital course. Repeated urinalyses were similar to the one on admission and an occasional renal failure cast was seen. The patient was placed on a low calcium diet on the fourth hospital day and a calcium balance study was attempted; however, because she had no bowel movements for the next few days, this study was not possible. During the last few days of hospitalization she became rapidly worse, with Kussmaul breathing and cyanosis. Calcium remained normal. Carbon dioxide combining power fell to 8.5 mEq./L.; phosphorus level did not change significantly; hemoglobin fell to 7.5 gm. per cent. She began to have muscular twitching and sinus tachycardia. The lungs remained free of rales. An immovable left shoulder and bilateral Babinski reflexes developed. The patient vomited occasionally and became progressively more disoriented; a marked uremic frost developed. Terminally her non-protein nitrogen was 425 mg. per cent; potassium, 4.6 mEq./L.; calcium, 9.6 mg. per cent; phosphorus, 21 mg. per cent. She died on the fourteenth hospital day.

CLINICAL DISCUSSION

DR. EDWARD REINHARD: I would like to summarize this complicated history very briefly. In 1935, during the third trimester of the first pregnancy, proteinuria, hypertension and slight ankle edema developed in this patient. She was delivered of a normal infant, and postpartum these findings disappeared. The patient remained asymptomatic for three years, following which the same sequence of events occurred during the third trimester of her second pregnancy. On this occasion she also noted periorbital edema in the mornings. Again she became asymptomatic following delivery. The patient was not examined between these two pregnancies. In 1942, during the last trimester of her third pregnancy, she again had proteinuria, hypertension, weight gain, mild headaches and shortness of breath. Labor was induced at term and she was delivered of a stillborn infant. There were no postpartum complications and the patient became asymptomatic. A year later a fourth pregnancy terminated in abortion during the first trimester. In 1945, the patient again became pregnant and because of increasing hypertension, proteinuria, ankle edema and headaches the pregnancy was terminated during the second month. The proteinuria, hypertension and headaches persisted, however. Six months later she noticed swelling of her face, hands, feet and legs. She had no sore throats, but her family physician made a diagnosis of tonsillitis and tonsillectomy was performed. She was told that her blood pressure was 170. Because of the persistence of edema she was admitted to Barnes Hospital and was found to have hypertension, anemia and proteinuria. Urine sediment contained many white and red blood cells and some casts. A diagnosis of chronic glomerulonephritis was made. In 1952 the patient began to have severe pains in her knees, hips, elbows, shoulders and back. Progressive anemia developed; nine blood transfusions were required during the year prior to admission. Approximately three or four months prior to the final admission anorexia, severe nausea and vomiting developed. By this time the patient had become confined to bed and chair because of her inability to move about. Dr. Glaser, we have emphasized many times in these Conferences that when a patient is seen with advanced uremia, it is impossible to identify the original renal lesion. However, on the basis of the history, would you like to hazard a guess as to the original type of renal disease?

DR. ROBERT GLASER: I would suspect that this patient had chronic glomerulonephritis. She had one episode that is very suggestive of the nephrotic syndrome which is consistent with the diagnosis of chronic glomerulonephritis.

It is conceivable, of course, that her renal disease began primarily as a result of toxemia of pregnancy. She had several episodes of pre-eclampsia but I do not know whether she ever had convulsions. I do not base the diagnosis of glomerulonephritis on the episode of tonsillitis later in her life. We would have to assume that if she had glomerulonephritis, it was probably the so-called type II which began insidiously without any recognizable episodes of acute glomerulonephritis. I believe that she will be found to have chronic glomerulonephritis.

DR. REINHARD: The patient had very marked calcification of her whole arterial system. At the time of death did she not also probably have considerable nephrosclerosis?

DR. GLASER: I am certain that she had nephrosclerosis, and unquestionably had secondary hyperparathyroidism as well as all of the many complications seen in chronic renal disease.

DR. REINHARD: Dr. Schroeder, do you have anything to add? How about the very high non-protein nitrogen?

DR. HENRY A. SCHROEDER: The high non-protein nitrogen suggests that the process had been going on for a long time. However, this course is not inconsistent with pyelonephritis, in spite of the episode of the nephrotic syndrome. The level of the non-protein nitrogen attained in this patient is usually considered inconsistent with life except in such chronic states as low grade pyelonephritis, polycystic disease and congenital abnormalities of the kidney.

DR. REINHARD: We may say, therefore, with complete assurance that on the basis of her metabolic disturbance the patient had very severe and advanced dysfunction both of the glomerular apparatus and of the tubular system. Dr. Porporis, would you now discuss the patient's interesting roentgenograms?

DR. ARTHUR A. PORPORIS: The roentgenograms were of interest for several reasons. There was cardiac enlargement. The anterior portion of the tenth rib on the right and posterior portion of the ninth rib on the left were involved by an expansile lesion, somewhat "soap bubbly" in appearance, which suggests hyperparathyroidism. Furthermore a rather diffuse demineralization of the bones was noted. There was striking calcification of all vessels including the aorta, renal, splenic, hepatic and inferior mesenteric arteries. The right kidney could not be visualized. However, the left kidney appeared to be markedly compromised in size with an estimated weight of approximately 100 gm. Soft tissue calcification in the fascial planes in the area of the left shoulder was seen. Roentgenographic evidence typical of hyperparathyroidism was observed in the hands where areas of subperiosteal bone resorption were observed. From the radiographic standpoint, one cannot distinguish primary hyperparathyroidism from secondary hyperparathyroidism. The findings are identical, but one clue which suggests secondary disease is the markedly reduced left renal mass.

DR. REINHARD: Dr. Sherry, during childhood this patient had an attack of joint pain diagnosed as inflammatory rheumatism, involving principally the left hip. In 1952 she began to have severe pains in her knees, hips, elbows, shoulders and back. These pains progressed until they completely incapacitated the patient and confined her to bed and chair. Could there be any connection between the latter pains and the pains experienced in childhood and if not what was the nature of the pain that developed in 1952?

DR. SOL SHERRY: I do not believe there is any relation between the pains in childhood and the more recent pains. I would be more inclined to explain the latter as part of the picture of hyperparathyroidism with the extraskeletal deposition of calcium in and around the joint spaces resulting in fixation of the joints.

DR. REINHARD: I would certainly agree. Let us review the chemical abnormalities in this patient's blood. Early in her hospital course, blood studies indicated several abnormalities including a profound decrease in CO_2 combining power, a marked elevation of the serum phosphorus, alkaline phosphatase and uric acid levels, and a decrease in serum protein, involving both albumin and globulin. A tremendous increase was found in the non-protein nitrogen. On the basis of these findings it seems clear that we are dealing with a profound metabolic disturbance which is consistent with renal failure and hyperparathyroidism, as several people have suggested already. The immediate problem is whether the patient had primary or secondary hyperparathyroidism. From the history it would seem obvious that she had renal disease first followed later by secondary hyperparathyroidism. We may review the chemical changes in the blood which lead us to say with complete assurance that this was secondary hyperparathyroidism. In primary hyperparathyroidism

patients have hypercalcemia, whereas this patient had a normal calcium. In uncomplicated primary hyperparathyroidism a low serum phosphorus is found, whereas this patient had a very high serum phosphorus. Acidosis is absent in primary hyperparathyroidism; whereas she had marked acidosis. We may therefore say that this patient had secondary hyperparathyroidism. We will devote the remainder of the discussion to a consideration of secondary hyperparathyroidism and the various types of osteonephropathy which may result from renal disease. Dr. Daughaday, what is the basic mechanism by which renal disease produces secondary hyperparathyroidism? Why does renal disease stimulate overactivity of the parathyroid gland?

DR. WILLIAM H. DAUGHADAY: If one reads Dr. Albright's monograph on the parathyroid glands and metabolic bone diseases and listens to Dr. Reinhard's summary, one would think that there never was any difficulty in distinguishing primary and secondary hyperparathyroidism. Actually, at the bedside, this is sometimes an extraordinarily difficult differential diagnosis and occasionally, as in a case described by Dr. Virgil Scott, both conditions may exist simultaneously.

DR. REINHARD: I merely said that the patient could not have uncomplicated primary hyperparathyroidism. Would you agree? If she had primary hyperparathyroidism due to a tumor, for example, there would have to be a complicating renal disease unrelated to the hyperparathyroidism.

DR. DAUGHADAY: I would agree with that. There is a good deal of confusion about parathyroid physiology, both as to the nature of the hormone, the fundamental action of the hormone and the regulation of hormonal secretion. The primary stimulus for parathyroid activity seems to be the level of ionized calcium in the plasma. When this is lowered, the parathyroid glands become hyperactive and act to return the lowered calcium to normal which Dr. Albright believes is performed largely by excretion of phosphate with a secondary increase in serum calcium. There is other evidence which would suggest that, if the calcium is maintained at a normal serum concentration, elevation of the level of serum phosphorus is a stimulus for parathyroid activity. In the present case, the factors which tended to lower serum calcium were an excessive loss of calcium in the urine, decreased intestinal absorption of calcium and a marked phosphorus retention. I would like to call attention to the chemical abnormalities noted nine years before her terminal illness when, although the non-protein nitrogen was reported as being 21 mg. per cent, the serum phosphorus was already elevated. Occasionally patients with glomerulonephritis or other type of nephritis are seen in whom there seems to be an inordinate elevation in serum phosphorus levels. The terminal stage of this patient's course was characterized by an extraordinary serum phosphorus level. In summary, parathyroid activity was probably increased in this patient because of a tendency toward a lowered serum calcium and the elevation of serum phosphate.

DR. REINHARD: From the literature one gets the impression that the stimulus for parathyroid hyperplasia is simply a decreased serum calcium level. As Dr. Daughaday has pointed out, this patient, at least during her terminal hospitalization, did not have a significantly lowered serum calcium. It seems, therefore, that a high serum phosphorus level can act as the stimulus for hyperparathyroidism when the serum calcium is normal. Dr. Daughaday, this patient showed a perfectly astonishing degree of calcification of the entire arterial system in spite of the fact that the serum calcium level was normal. I presume that here, also, the important factor is the high serum phosphorus. Would you comment on the mechanism of deposition of calcium in the arterial system under these circumstances.

DR. DAUGHADAY: The prerequisites for pathologic calcification are present here; namely, a very high ion product of calcium and phosphorus. We should not look upon this product too literally in terms of a solubility product in the usual physical-chemical sense. However, from the clinical standpoint, when this situation exists, pathologic calcification is almost sure to follow. What are the shock areas of the body which are subject to pathologic calcification? In general, any acid excreting organ is particularly prone to pathologic calcification; namely, the lungs that excrete CO_2, the stomach which excretes hydrochloric acid, and the kidney which normally excretes acid in the formation of an acid urine. The media of the arteries and cartilage have high binding affinities for calcium and phosphate and are subject to pathologic calcification. The patient we are discussing was in an unstable metabolic state mobilizing calcium from bone and depositing these calcium

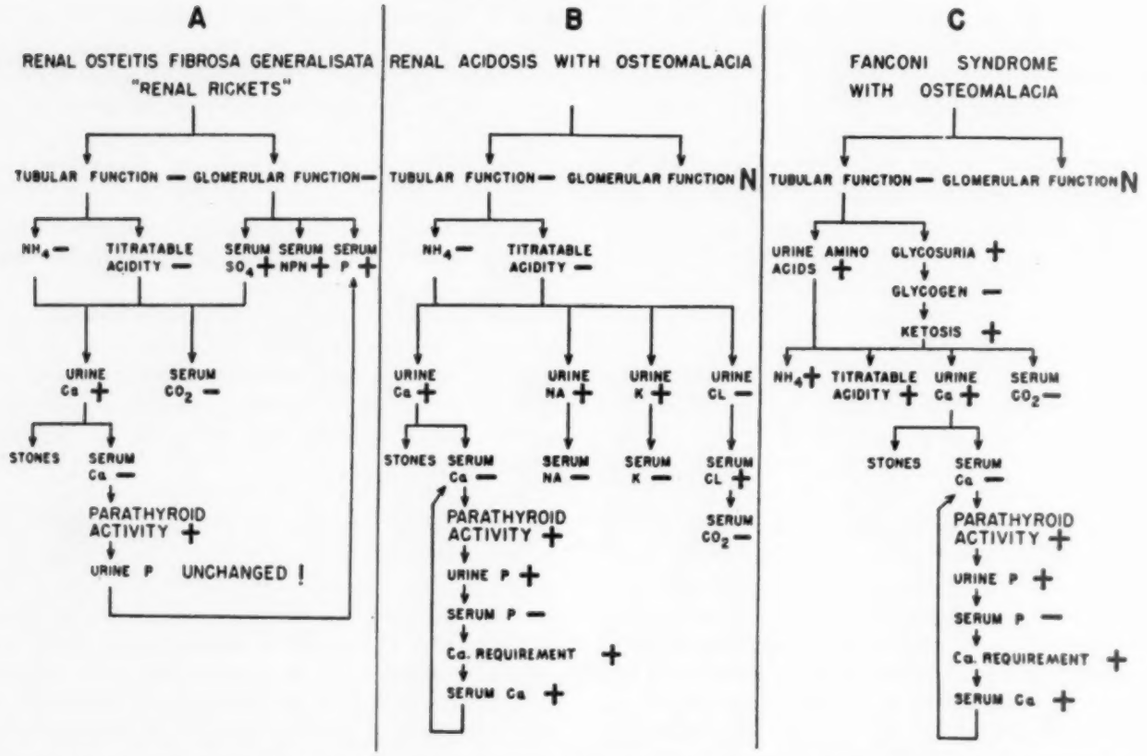

FIG. 1. Schematic diagram of differences in the sequence of events in three types of secondary hyperparathyroidism. From Reifenstein, E. C., Jr. Diseases of the parathyroid gland. In: Textbook of Endocrinology, edited by R. H. Williams. Philadelphia, 1955. W. B. Saunders Co.

salts in the arteries and other tissues of the body.

DR. REINHARD: Dr. Schroeder, would you comment on the pathologic nature of the vascular lesions in this patient.

DR. SCHROEDER: The lesions will probably be medial in location. I suspect they will be a variety of Mönckeberg's sclerosis.

DR. SHERRY: The general change will be a Mönckeberg's sclerosis although accompanied by considerable intimal calcification.

DR. REINHARD: It is believed that there are three varieties of osteonephropathy, and in each variety there is hyperparathyroidism secondary to a different type of disturbed pathologic physiology in the kidney. Figure 1 is, perhaps, familiar to many of you. It is taken from William's Textbook on Endocrinology and illustrates the sequence of events in the three varieties of osteonephropathy. On the left (column A) there is a schematic representation of renal osteitis fibrosa generalisata, so-called renal rickets—a variety of osteonephropathy which develops when there is marked glomerular disease as well as marked tubular dysfunction. Column B outlines the schematic representation of renal acidosis with osteomalacia, a variety of osteonephropathy which develops when there is renal tubular dysfunction. According to Reifenstein this type involves chiefly the distal convoluted tubules but with some glomerular insufficiency. Column C lists the Fanconi syndrome with osteomalacia due to tubular dysfunction involving chiefly the proximal convoluted tubules. Again, there is little glomerular disease. Perhaps this table is an oversimplification of the problem. On the other hand, I thought it might be well to review the metabolic disturbances that accompany each of these conditions. On the basis of the x-ray findings we may conclude that the patient had osteitis fibrosa generalisata. We would also say that the patient had renal rickets on the basis of the electrolyte changes. Dr. Daughaday, would you discuss the electrolyte changes which occur under these various circumstances?

DR. DAUGHADAY: Let us focus our attention on the serum levels listed in the third line of column A. You will notice that the serum phosphorus level is markedly elevated. The

serum non-protein nitrogen is also elevated with an associated metabolic acidosis. These are the findings in the present patient. In comparison, note the serum levels in column B in which the characteristic changes are a low serum phosphorus and a relatively normal serum calcium and in addition there may also be a low serum potassium. Both columns A and B are characterized by a lowering of the CO_2, so the difference in the serum phosphorus is of great importance in the differential diagnosis. Also, in renal acidosis with osteomalacia, the non-protein nitrogen tends to be normal. As for the calcium and phosphorus levels in Fanconi's syndrome the situation is very much the same. Fanconi's syndrome differs from renal acidosis with osteomalacia in that there is marked amino aciduria and renal glycosuria. Ketosis frequently occurs with an increased load of organic acids in the urine. The non-protein nitrogen is usually normal. In all three situations, parathyroid activity is increased. In renal acidosis, where phosphorus is retained, the parathyroid hormone can no longer promote the excretion of urinary phosphorus. The situation in renal osteomalacia is different, because increased urinary phosphorus excretion is possible leading to an undersaturated serum with respect to calcium and phosphorus. The serum calcium is maintained by increased parathyroid activity. The interrelation of parathyroid function to phosphorus metabolism is essentially the same in the Fanconi syndrome.

DR. REINHARD: Dr. Schroeder, this patient had advanced calcification of the large arteries of the body, many of the medium-sized arteries and even some small arteries. Nevertheless, she did not have what is often thought of as the arteriosclerotic type of hypertension. In fact, she had a very labile blood pressure. On October 17th, for example, her blood pressure dropped within a matter of a few hours from 200/140 to 130/85. How do you account for this lability in the blood pressure in the face of severe calcification of the arterial system?

DR. SCHROEDER: I do not believe anyone has reported hypertension dependent upon organic arterial disease so generalized that it gave a fixed diastolic hypertension.

DR. REINHARD: Is it not true that many very old people with severe arteriosclerosis will have a blood pressure in the vicinity of 180/80?

DR. SCHROEDER: That is true. It is probably due to a loss of elasticity in the aorta and in the large muscular vessels. In this case there seems to be involvement of the medium-sized and smaller arteries. The major resistance to blood flow in the arterial tree is in the smaller vessels, that is, in the tertiary branches, terminal arteries and arterioles. It is actually greater in the smaller arteries than in the arterioles. I believe that the type of hypertension which this patient had is probably in large measure a retention hypertension from metabolic products in her blood acting on small arteries and arterioles rather than an anatomic or true renal hypertension.

DR. REINHARD: Why was the hypertension so labile?

DR. SCHROEDER: We cannot explain lability in blood pressure in patients who have severe azotemia except by saying that there are many mechanisms operating which make the blood pressure go up as well as down.

DR. REINHARD: Is it common to have this lability?

DR. SCHROEDER: It is common to have lability in a patient who has not had diastolic hypertension before azotemia. It is possible that increased cathecol amines and other pressor substances in the blood in such persons are involved in this mechanism. Of course, the usual homeostatic mechanisms are also active and they are probably responsible for the lability.

DR. REINHARD: The house staff final diagnoses were: chronic glomerulonephritis with uremia; secondary parathyroid hyperplasia; osteitis fibrosa cystica generalisata; renal osteodystrophy and generalized arteriosclerosis. I agree with these diagnoses and would only add that the patient almost certainly had nephrosclerosis as well at the time of death. Although I agree that the original renal lesion was most likely glomerulonephritis, she may also have had pyelonephritis.

PATHOLOGIC DISCUSSION

DR. WILLIAM R. MURPHY: The total weight of both kidneys was 125 gm. Increased pelvic fat suggested even further reduction in renal parenchyma beyond that indicated by the weight. The surfaces of the kidneys were uniformly and finely nodular. The cortex was greatly reduced in thickness. Several large retention cysts were present, probably an incidental finding. Calcium was not recognized grossly in the renal parenchyma, and stones were not found in the pelvis or lower urinary

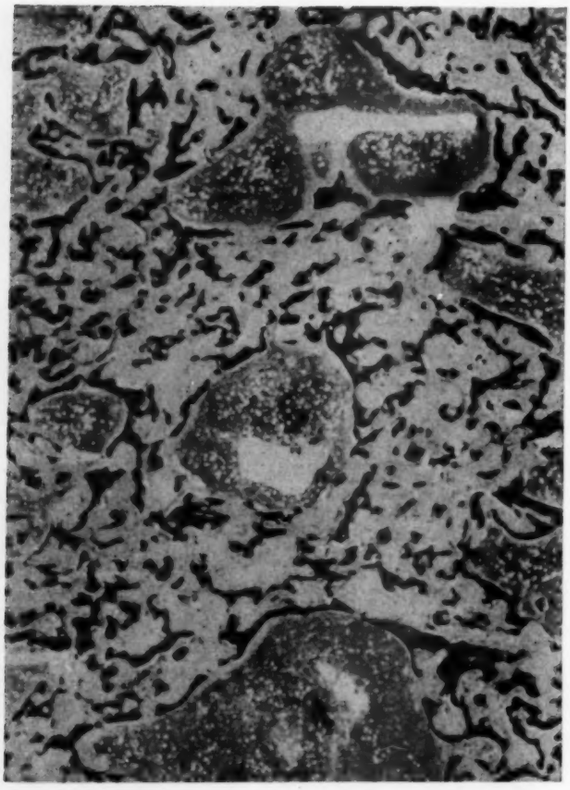

FIG. 2. Vertebra, irregular bony trabeculae surround the pale fibrous marrow leaving zones of cellular marrow that contain no bone; hematoxylin and eosin stain, approximately × 4.

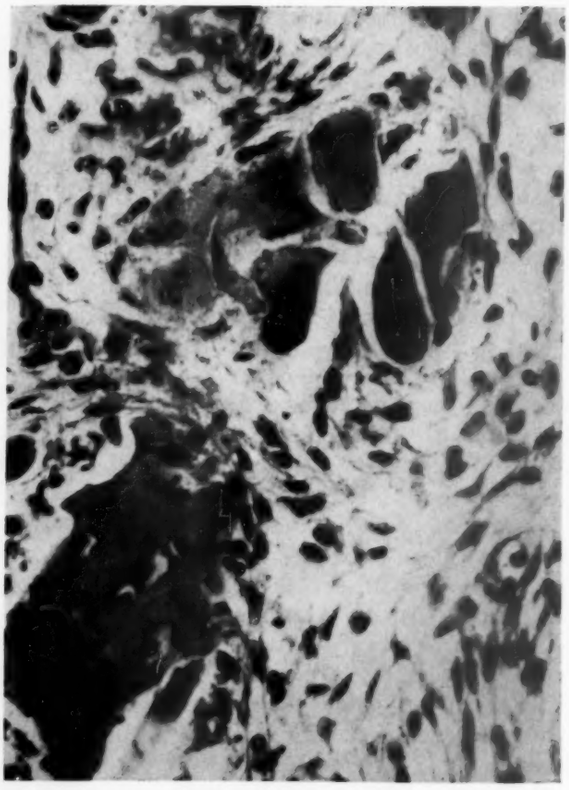

FIG. 3. Vertebra, prominent osteoclastic activity; Masson tri-chrome stain, approximately × 250.

tract. The pelves of the kidneys were rather thin, not roughened or thickened.

Three parathyroid glands were found. Each measured at least 1 cm. in its greatest diameter. The upper parathyroids were located behind the lobes of the thyroid. They were somewhat smaller than the lower, in contrast to the usual finding in primary hyperparathyroidism where the upper parathyroids are often several times larger than the lower. The entire weight of the three parathyroids was 1,500 mg., about ten times the normal weight. The cut section was smooth, homogeneous and pale gray.

There were numerous changes in the bones. Fractures had occurred in the neck of the left femur and in the pelvis. The cortex of the bone was fragile and could be easily broken under slight pressure. The lumbar vertebrae showed loss of substance. There were focal zones that were light red, glistening, and contained no bone trabeculas. In the tenth rib near the costochondral junction, a yellowish gray mass filled the bone and extended to the margins of the expanded cortex. A similar lesion was present in the opposite tenth rib at about the same location. The lesion demonstrated radiographically in the seventh rib was not recognized at autopsy. In the skull there was complete loss of the bony tables and obliteration of the diploë.

All arteries had undergone advanced calcification of the media. Despite this involvement of the coronary and renal arteries, significant narrowing of the lumens was not present. Firm nodular areas were present in the peripheral parts of all lobes of the lungs. The stomach and duodenum had no ulcers or scars. Mucosal calcification was not recognized. The heart weighed 350 gm. and was not otherwise remarkable.

DR. JAMES C. HARKIN: The classic lesions of hyperparathyroidism were manifest in the bones. Such severe changes are more often found in cases of primary rather than secondary hyperparathyroidism.

In the vertebrae, the trabeculae were moderately thick, had a complex pattern and were calcified. The majority of the marrow space was comprised of dense fibrous tissue. Scattered foci

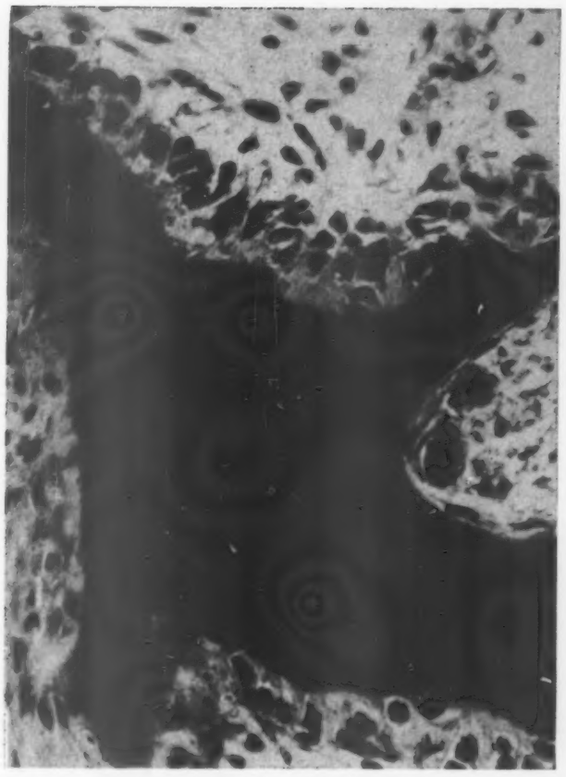

FIG. 4. Skull, osteoblastic activity; hematoxylin and eosin stain, approximately × 250.

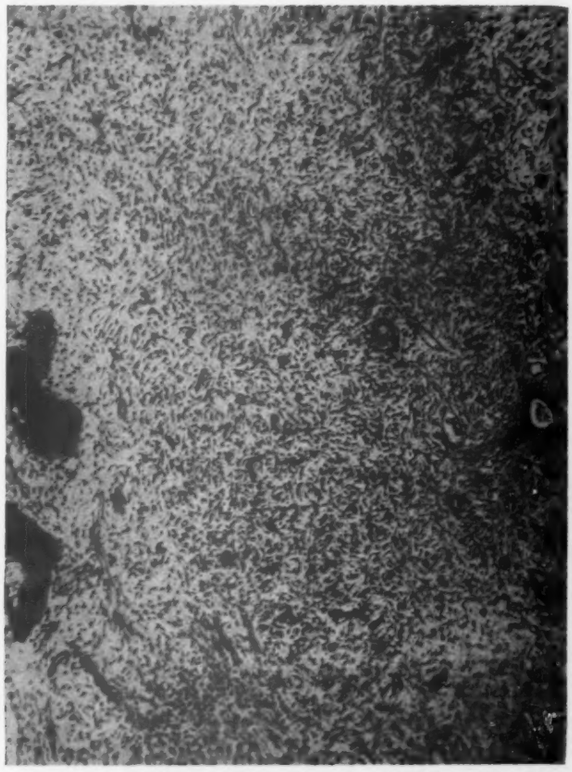

FIG. 5. Pseudo-tumor of rib; hematoxylin and eosin stain, approximately × 42.

without trabeculae were filled with cellular marrow. (Fig. 2.) Numerous osteoclasts surrounded trabeculae. (Fig. 3.) In a few sites there was evidence of new bone formation as characterized by calcified trabeculae encased in a sheath of osteoid with peripheral osteoblasts. (Fig. 4.)

The calvarium was considerably thickened. On section, from inner to outer surface the bone had a uniform pattern of irregular trabeculae and fibrous tissue. The original osseous plates encasing the marrow-containing diploë were obliterated.

In the long bones the pattern of irregular trabeculae and fibrous tissue was present in the cancellous bone and in the inner aspects of the thinned cortex. The size of the central marrow cavity had not been materially reduced. At the junction between marrow and altered bone, iron-containing macrophages were identified.

The lesion most reminiscent of the cysts of von Recklinghausen's disease was the one in the rib. A fibrous nodule containing only a few spicules of bone involved and expanded the cortex. (Fig. 5.) A few giant cells were associated with the interlacing spindle cells. There were no bone cysts filled with myxomatous connective tissue, as seen in classic instances of osteitis fibrosa cystica.

The bony spicules in this case of secondary hyperparathyroidism afford a striking contrast to the uncalcified osteoid trabeculae of vitamin D deficiency rickets. In renal hyperparathyroid osteitis fibrosa in children, occasionally somewhat inaccurately termed renal rickets, epiphyseal abnormalities occur; but as in this case in the adult, there is actually an abundance, rather than a deficiency of minerals to form bone from the osteoid spicules. However a true renal rickets does occur in Fanconi's syndrome in which excessive renal loss of phosphorus occurs. The bone changes of Fanconi's syndrome are morphologically similar to rickets and not to hyperparathyroidism. The mechanism of injury in hyperparathyroidism apparently follows a direct action of the hormone on bone as well as its renal and possible general cell-membrane functions.

In the case under consideration the three parathyroids were similar. Nodules of oxyphil and

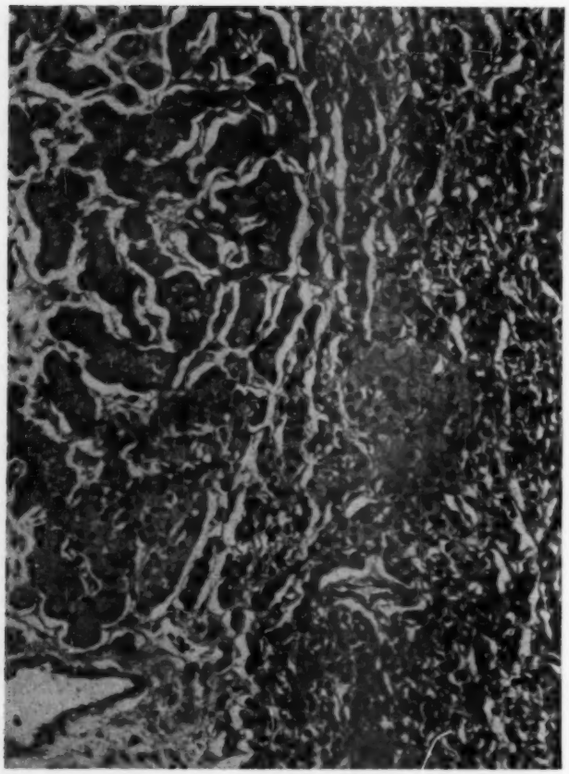

FIG. 6. Parathyroid, columns of cells arranged in nodules and sheets; a clump of oxyphil cells have gray cytoplasm; hematoxylin and eosin stain, approximately × 100.

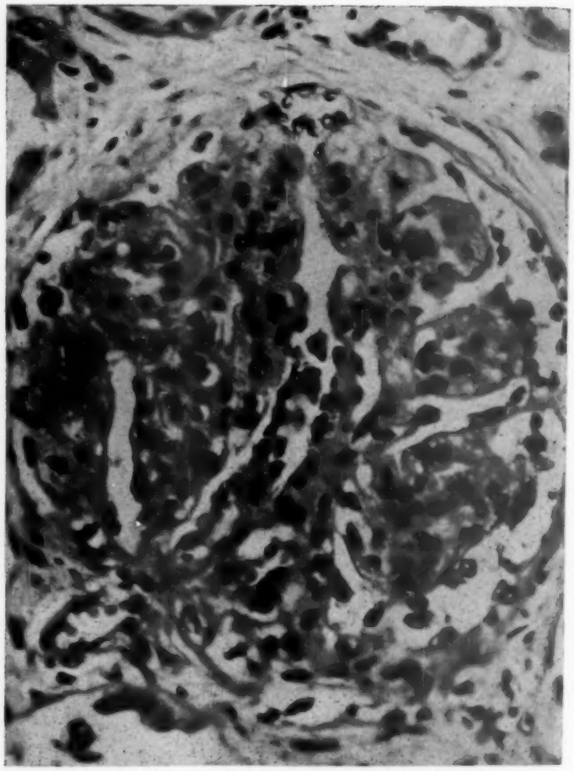

FIG. 7. Glomerulus, proliferation of tuft and focal calcification; hematoxylin and eosin stain, approximately × 250.

chief cells were present. (Fig. 6.) These masses were neither more cellular than the adjacent gland nor did they particularly compress it. Large or unusual nuclei were not identified. A few cells had more abundant clear cytoplasm, but large wasserhelle cells were not present.

The kidneys were so severely scarred that there was some uncertainty as to the original lesion. Changes consistent with the diagnoses of chronic glomerulonephritis and of acute and chronic pyelonephritis were present. The entire kidney, but particularly the cortex, appeared to represent an extensive cicatrix from which only scattered nephrons had escaped. Even the remaining glomeruli had changes, such as increased cellularity and proliferation of the epithelium of the capsule and glomerular tuft. (Fig. 7.) In some of the scarred glomeruli there was a lobular pattern of hyalinization.

Metastatic calcification was extensive. The basement membrane of some renal tubules was calcified. (Fig. 8.) In others the masses of calcium were more bulky and were associated with disruption of cells. Crystalline casts occluded the lumens of still other tubules. Striking calcification of the media of arteries of all sizes was present, not only in the kidney but also in other organs. There was only slight intimal thickening. The larger vessels throughout the lungs were calcified. Calcification of the alveolar walls varied considerably, but was marked in some regions. (Fig. 9.) A polymorphonuclear exudate filled many of the bronchi and terminal air spaces. In the stomach only a few microscopic foci of mucosal calcification were present. The small vessels of the dermis and subcutaneous tissue were the seat of severe calcification. Adjacent to acute ulcers that extended through the dermis several vessels contained organizing thrombi.

In summary, this patient had renal hyperparathyroid osteitis fibrosa with unusually extensive bone lesions. It seems reasonable to assume that the original renal disease was accelerated in its severity by the superimposition of nephrocalcinosis and infection. Here, as in most cases of secondary hyperparathyroidism, renal stones were not present.

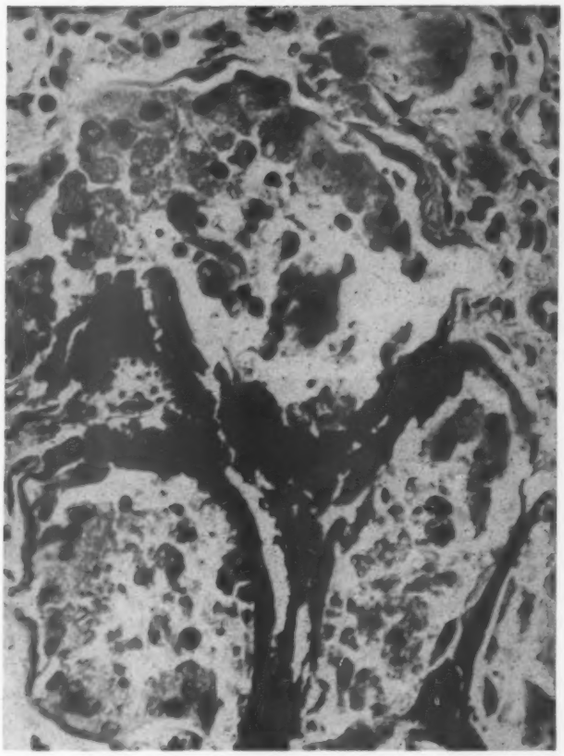

FIG. 8. Renal tubules, calcification of basement membranes and disruption of epithelium; hematoxylin and eosin stain, approximately × 250.

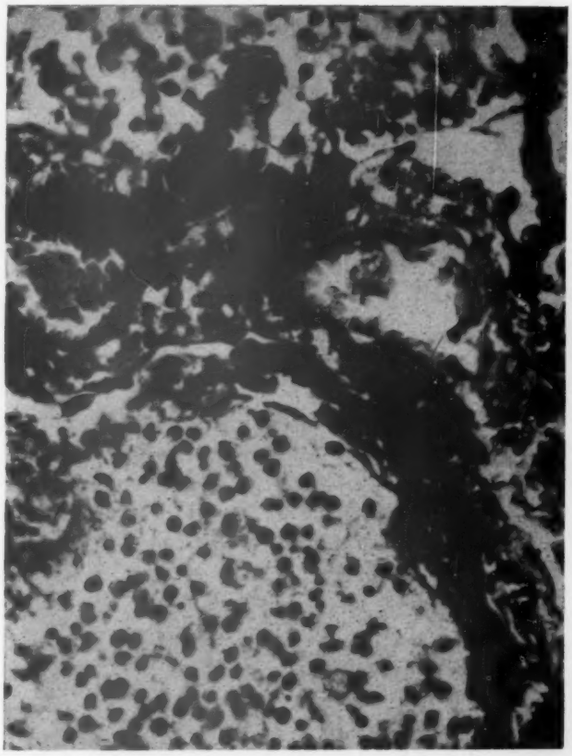

FIG. 9. Lung, calcification of vessel and of alveolar wall; in the lower portion of the photograph alveolus is filled with exudate; hematoxylin and eosin stain, approximately × 250.

DR. DAUGHADAY: I would like to add two final comments. The first concerns clubbing in hyperparathyroidism with osteitis fibrosa cystica. Such clubbing is not true clubbing; it is due to the telescoping of the terminal phalanges of the fingers secondary to bone resorption. The last comment I should like to make is that the evidence in favor of the direct parathyroid action on bone is, I believe, almost inescapable. If the renal function is relatively normal, one can explain most of the clinical features of hyperparathyroidism on the basis of a predominant action of the parathyroid hormone in increasing phosphorus excretion by the kidney. When renal function is grossly impaired, the direct effect of the parathyroid hormones on bone becomes more and more evident. I have seen a patient with hypercalcemia and hyperphosphatemia in secondary hyperparathyroidism. Similar cases have been reported in the literature. In these unusual patients, hyperparathyroidism is overcompensating in respect to serum calcium. This situation is rare, to be sure, but it is almost inexplicable without invoking a direct action of the parathyroid hormone on bone.

DR. SHERRY: Dr. Daughaday, this patient had an ulcer or an ulcer type syndrome several years before death. I wonder whether the milk which she drank at that time for her ulcer may have contributed significantly to the amount of metastatic calcification that she presented at autopsy.

DR. DAUGHADAY: It may be a contributing factor. One could explain everything on the basis of the renal lesion alone but any excess calcium and phosphate intake would aggravate the situation.

Acknowledgment: Photomicrographs were prepared in the Department of Pathology, Washington University School of Medicine.

Research Society Abstracts

Association for the Study of Liver Diseases

ABSTRACTS OF PAPERS PRESENTED AT THE SIXTH ANNUAL MEETING, CHICAGO, ILLINOIS, NOVEMBER 3, 1955

CARBOHYDRATE METABOLISM. *Philip K. Bondy.* Yale Medical School, New Haven, Conn.

The role of the liver in carbohydrate metabolism cannot be considered independently since it is intimately associated with the synthesis and degradation of protein and fats. Inevitably, alterations in the metabolism of any one of these classes of substances will cause derangements in the metabolism of the others.

One of the chief functions of the normal liver is the maintenance of a normal blood glucose concentration, both by removing excess glucose from the blood when the concentration is elevated and by secreting glucose when it is low. When glucose is injected intravenously into normal persons, it is rapidly removed from the blood which traverses the splanchnic vascular system. The rate of removal can be estimated, after catheterization of the hepatic vein, by multiplying the arteriohepatic venous glucose difference by the splanchnic blood flow. In a series of subjects studied in this manner the splanchnic system was capable of removing from 6 to 11 mg. of glucose per kg. of body weight per minute. At the height of the arterial glucose rise the rate at which glucose left the blood throughout the body could also be estimated by assuming that 4 per cent of all the extracellular glucose is removed per minute. The rate constant 0.04 used in this assumption is derived from studies of the rate of disappearance of glucose from the blood after intravenous injection and represents a generous estimate, since in most studies the rate constant observed for normal persons is less than 3 per cent per minute. The peak rate of removal of glucose by the splanchnic system was, in all instances, at least 25 per cent greater than that needed to account for the rate of disappearance of glucose for the entire body. The normal splanchnic system (that is, in this case, chiefly the liver) is, therefore, capable of removing glucose from the blood, if necessary, at a much higher rate than it is ever likely to be called upon to achieve.

The glucose thus accumulated by the liver may be stored as glycogen or broken down by two major pathways, the anaerobic Meyerhof-Embden pathway and the oxidative hexose-phosphate shunt. The latter results in formation of pentose ribose phosphate which may follow several pathways, including incorporation into nuclei acids, or condensation with another molecule of ribose to form a triose plus a seven-carbon sugar which later may recondense with the triose and reform a hexose and a four-carbon sugar. The relative importance of the two pathways varies from tissue to tissue. Thus, whereas most of the carbohydrate breakdown in brain occurs by way of the Meyerhof-Embden anaerobic pathway, in the liver probably only about one-third of the glucose is broken down in this way, the remaining two-thirds probably passing through the phosphogluconic acid shunt. The oxidative pathway in the liver is therefore of great importance.

The liver maintains normal glucose concentrations by secreting glucose as well as by removing it from the blood. When the chief non-glucose hexoses of food, galactose and fructose enter the liver they are phosphorylated by specific enzymes and converted by way of glucose-1-phosphate to glycogen, or via glucose-6-phosphate to free glucose. Since the only form of hexose monophosphate which can be hydrolyzed in the liver to the free hexose is glucose-6-phosphate, any hexose which enters the liver cell is converted into a glucose precursor. Under fasting conditions, the liver constantly secretes glucose into the hepatic vein. The quantity secreted has been estimated for various animals, including man, by a number of different technics. Estimates vary from about 2 mg. per kg. per minute for the dog and man to 6 mg. per kg. per minute for the rat. The glucose arises from preformed glycogen, from dietary hexoses and by

glucogenesis from deaminated amino acid residues, from certain pentoses via the hexose monophosphate shunt, and even, potentially, from fatty acids by way of acetyl-CoA, the Krebs cycle and retrograde progression up the anaerobic glycolytic series of reactions to form glucose-6-phosphate. Since the series of reactions involved in this pathway is entirely reversible, any continuing demand for glucose secretion by the liver may sweep amino acids, hexoses, pentoses and even fatty acids into the blood in the form of glucose. In severe liver failure, when maintenance of blood glucose requires the remaining relatively intact liver cells to release glucose at a maximal rate, many other functions of the liver cell may be sacrificed. Thus protein synthesis, fatty acid synthesis, nucleoprotein formation and the formation of numerous materials such as urea and cholesterol, which are derived indirectly from the tricarboxylic acid cycle or its precursors, may be sacrificed to maintain the blood glucose at its normal level.

Hepatic insufficiency might therefore be expected to produce several abnormalities directly or indirectly associated with abnormalities of carbohydrate metabolism. One might anticipate, for example, that clearance of glucose from the blood would be slower than normal after administration of a glucose load; indeed, this "diabetic" glucose tolerance curve is sometimes observed. The difficulty here is not, however, true diabetes, since the condition is not ameliorated by insulin. In the inadequate liver one might also expect to observe difficulties in the secretion of sufficient glucose to maintain a normal level of blood sugar. Although spontaneous hypoglycemia does occasionally occur in severe liver failure, this is rare. Myers, in studying a group of patients with cirrhosis by liver catheterization, found that normal amounts of glucose were secreted, and Zimmerman found that less than 1 per cent of patients with cirrhosis suffered from hypoglycemic attacks.

Reduction of the availability of essential intermediates of the tricarboxylic acid cycle might interfere with the synthesis of urea, since α-ketoglutarate is a precursor of glutamic acid, itself a precursor of ornithine. The resulting abnormalities of ammonia metabolism, which have been described in severe cirrhosis, will be discussed by another member of this symposium. Moreover, unavailability of ribose and the tendency of amino acids to be deaminated and used as carbohydrate precursors might be expected to reduce protein synthesis, with resulting deficiencies of certain specific proteins formed in the liver such as serum albumin and resulting deficiencies of general tissue repair where ribose nucleic acids are necessary. The well known failure of the failing liver to form physiologic amounts of albumin and the association of hepatic failure with anemia, gastrointestinal ulcerations and slow wound healing may be reflections of this deficit. These subjects will also be discussed in more detail later in this symposium.

Although the liver is of great importance in the maintenance of normal carbohydrate metabolism, most of the disturbances resulting from hepatic failure are manifested not by alterations of the carbohydrate metabolism itself but by disturbances of the closely associated metabolism of proteins and lipids.

PROTEIN METABOLISM IN SEVERE LIVER DISEASE, ESPECIALLY ALCOHOLICS WITH CIRRHOSIS. *Charles S. Davidson.* Harvard Medical School, Boston, Mass.

The fact under discussion is that severe protein undernutrition is a regular accompaniment of severe cirrhosis of the liver. In discussing a problem of nutrition, the following four factors must be considered: (1) reduced food intake, (2) impaired digestion and absorption, (3) altered intermediary metabolism and (4) increased excretion. These will be considered briefly and separately.

No doubt most alcoholic patients with cirrhosis have been consuming for some time a diet inadequate in protein. On this basis protein undernutrition is not a surprising observation. Whether or not diminished food intake accounts for the protein undernutrition seen in persons with chronic cirrhosis is unknown, but some evidence exists that it does not. Thus clinically it is our impression that recovery to normal protein nutrition takes longer and is more difficult to achieve than in a similarly undernourished person without liver disease. This concept requires substantiation. If one assumes that it is true, then diminished food intake cannot account for all the protein undernutrition present in persons with liver disease.

Impaired digestion and absorption might be expected when portal hypertension is present due to edema of the gastrointestinal tract and to possible decreases in enzymes, bile and, in some patients with pancreatitis, pancreatic secretion.

However, the stool nitrogen and fecal calorie content in patients with cirrhosis who are known to be on protein diets or who have no protein intake at all do not differ from those of normal subjects on the same diets to any significant degree. Thus total nitrogen and calorie absorption appears to be essentially normal; presumably digestion and absorption cannot account for any significant proportion of the protein undernutrition seen in chronic cirrhosis.

Increased excretion of nutrients does occur, but probably is not a limiting factor. Urinary excretion of amino acids increases in most patients with disease of the liver but neither total amino acid excretion nor loss of individual essential amino acids is considered sufficient to disturb nutrition. Furthermore, it is possible to achieve positive nitrogen balance in persons with chronic liver disease, but this sometimes requires a higher nitrogen (protein) intake than that for a normal person similarly undernourished, and nitrogen balance sometimes becomes more positive as disease of the liver subsides. This is due to decreased urinary nitrogen excretion (mostly urea).

This leads to the consideration of altered intermediary metabolism. As previously noted, recovery to normal nutrition probably takes longer than it should and seems to depend upon improvement in the function of the liver, that is, improvement in nitrogen balance often occurs as disease of the liver subsides. A defect in albumin synthesis is well known and diminishes as evidence of disease of the liver subsides. A consideration of the metabolism of amino acids reveals that some defects are certainly present in disease of the liver, although many of the metabolic pathways through which amino acids must pass in the body have not been studied in this condition. For example, the rate of removal of amino acids from the circulation by the cells, studied so carefully by Christianson in experimental animals, is not known in disease of the liver in man. Similarly, the rate of synthesis of amino acids to new tissue protein has not been studied nor has the synthesis of peptides with the exception of glutathione which appears to be decreased in the red blood cells of many patients with severe disease of the liver. The metabolism of a few specific amino acids has been studied. A reduction appears to occur in the rate of removal of glycine from the blood after it is administered. Abnormalities in methionine, cystine and cysteine metabolism have also been observed. Watson, Kinsell, and Sherlock and Summerskill have shown that methionine has toxic effects in disease of the liver, the latter two authors being able to prevent these toxic effects by simultaneous administration of oxytetracycline. Walshe found methylmercaptan and dimethylcystine in the urine of a patient with fetor hepaticus, which presumably arose from a defect in sulphur amino acid metabolism. The blood phenol concentration is often elevated in patients with disease of the liver, suggesting the possible existence of an abnormality in tyrosine and phenylalanine metabolism. Moreover, an increased pigmentation occurs on many occasions in patients with chronic cirrhosis, which might be related to abnormal tyrosine metabolism. Certainly in some patients with severe disease of the liver a marked increase in glutamine occurs in the blood, and Walshe has shown (by paper chromatography) abnormalities in some of the other amino acids, particularly in patients in hepatic coma. Finally, urea formation from ammonia, which occurs entirely in the liver, is abnormal in some patients with severe disease of the liver who have been given ammonia. This can be seen obviously in the hepatectomized animal and may be related to hepatic coma. The metabolism of ammonia in these patients will be discussed in the next presentation.

AMMONIUM METABOLISM. *Leslie T. Webster, Jr.* Western Reserve Medical School, Cleveland, Ohio.

Ammonium metabolism was studied in patients with and without cirrhosis. No evidence of mental disturbance, tremor, hemorrhage, shock or azotemia was present unless specifically referred to herein. Ammonium nitrogen (NH_4-N), measured by the Conway microdiffusion technic, was determined in blood drawn approximately simultaneously from peripheral vein, artery, internal jugular vein, superior jugular bulb and abdominal collateral vein. The effects of fasting, intravenous urea, oral protein and oral diamox® on blood NH_4-N concentrations were studied to elucidate some of the sites which contribute or remove NH_4-N (or a related substance) from the blood.

In fasting patients with or without cirrhosis repeated blood samples drawn during the day from a given vein contained approximately the same NH_4-N concentration; all observations were made after a twelve hour fast. Higher

NH_4-N concentrations in fasting jugular bulb blood than arterial or jugular venous blood indicated that brain contributed NH_4-N to the circulation in patients with or without cirrhosis.

A prompt rise in abdominal collateral venous blood NH_4-N concentration occurred in three patients with cirrhosis during infusions of urea. In one instance this effect was prevented by oral neomycin, indicating that the urea yielded NH_4-N in the gastrointestinal tract, presumably as a result of bacterial action. Similar rises also occurred after a 50 gm. protein meal and after 10 gm. of oral L-glutamine but were not prevented by neomycin. No rise was observed after oral amino acids (methionine, lysine, glycine, arginine, tyrosine, isoleucine and valine) or after oral NH_4Cl which contained more NH_4-N than that in any of the other N substances given. Thus in patients with cirrhosis, these observations suggested that one source (which does not eliminate others) of increased blood NH_4-N concentrations after protein ingestion is the amide N of glutamine contained in protein. This NH_4-N is absorbed by the small intestine and its formation does not depend on bacterial action.

Both in hepatic coma and after diamox administration NH_4-N uptake by the extremities was usually observed. (Diamox is a carbonic anhydrase inhibitor which does not liberate its nitrogen in the body and may induce impending hepatic coma associated with increased peripheral venous blood NH_4-N concentrations in susceptible patients with cirrhosis.) One hour after the diamox was administered orally increases in brain NH_4-N output occurred (increased jugular venous blood NH_4-N concentrations). These increases occurred less frequently in nine patients without disease of the liver, were more marked in sixteen with cirrhosis, and were greatest in one with cirrhosis in whom impending coma developed, although two patients with prior signs of impending coma showed rises comparable to those of the group with cirrhosis. Similarly, the brain was thought to contribute NH_4-N in two comatose patients without disease of the liver and in five patients in hepatic coma, selected because none had hemorrhage, shock or azotemia.

In contrast, a relative uptake of NH_4-N by brain followed intravenous NH_4 salt, intravenous urea, or oral protein (one patient with cirrhosis) and also frequently occurred in four patients in hepatic coma with hemorrhage, shock or azotemia. Thus it appeared that in patients in hepatic coma, brain could remove NH_4-N added to the circulation in some instances or contribute excess NH_4-N as a result of disordered metabolic function in others.

METHIONINE TOXICITY IN LIVER DISEASE AND PREVENTION BY CHLORTETRACYCLINE. *Sheila Sherlock, Elizabeth A. Phear, B. Ruebner and W. H. J. Summerskill.* Postgraduate Medical School of London, London, England.

Oral methionine caused neurologic deterioration in seven of nine patients with portal cirrhosis and chronic portal systemic encephalopathy. In eight of the nine patients large portalsystemic venous collateral channels were demonstrated. It was without effect in seven patients with cirrhosis of the liver, three of whom had extensive portal systemic circulation and one of whom had extrahepatic portal vein obstruction. These patients had never experienced neurologic complications.

Intravenous methionine was without effect in three of those who reacted to the oral amino acid and in one a delayed exacerbation occurred. Neurologic deterioration occurred without significant change in blood ammonium, blood pH or serum bilirubin levels. Blood methionine levels rose equally in those in whom deterioration occurred and in those in whom it did not.

Oral chlortetracycline prevented or delayed neurologic deterioration in five sensitive patients who received it, despite comparable blood methionine levels. The fecal flora of patients with disease of the liver and neurologic complications did not differ from that of normal subjects and patients with uncomplicated cirrhosis. Methionine did not change the fecal flora, but in the patients in all groups administration of chlortetracycline resulted in an increase in proteus with elimination of bacteroides and an inconstant fall in Bacterium coli. The streptococcal types changed and lactobacilli increased. *In vitro* ammonium production by proteus, Bact. coli and bacteroides was small and was unaffected by chlortetracycline.

The toxicity of methionine in patients with chronic portal systemic encephalopathy is due to some breakdown product of methionine which is not ammonium. It is suggested that chlortetracycline may be of benefit in spontaneous "hepatic coma."

ADDITION OF THIOCTIC ACID TO A PLAN FOR MANAGEMENT OF HEPATIC INSUFFICIENCY. *Charles*

M. Thompson, Joseph M. Gambescia, Philip Lisan and Morton Fuchs. Hahnemann Medical College, Philadelphia, Pa.

In hepatic coma elevated blood ammonia levels have been repeatedly observed. High blood and spinal fluid levels of glutamine, methionine sulfoxide and amino aciduria indirectly suggest marked alteration in the metabolism of nitrogenous compounds.

Evidence also exists of an interruption in intermediate carbohydrate metabolism. This is indicated by elevations of blood lactic acid, pyruvic acid and alpha-ketoglutaric acid. It could be postulated that failure of an enzyme system or systems could account for the elevated blood levels of these metabolites. The failure of an enzyme system to facilitate the aerobic oxidative decarboxylation of alpha-keto acids and the transference of decarboxylated pyruvic acid into the Krebs cycle could be one result of hepatic insufficiency.

Thioctic acid (lipoic acid, pyruvate oxidation factor, protogen, and the like) is one of the more recently recognized biocatalysts, and has now been synthetized in pure form. The nutritionally effective form of thioctic acid is a complex of thioctic acid and thiamin. This molecular conjugate appears to have an essential role in the oxidation of alpha-keto acids and in the transference of pyruvic acid into the Krebs cycle.

First, a group of patients who showed no evidence of disease of the liver were studied, and diurnal variations in the blood pyruvic acid and lactic acid levels in relationship to time of day, diet or exercise were recorded. No effect of thioctic acid on normal blood pyruvic and lactic acid levels was noted. A group of patients who showed evidence of hepatic insufficiency marked by torpor or coma and normal or elevated blood pyruvic acid and lactic acid levels were then followed and an aggressive plan for management instituted. No change in the level of blood metabolites in the majority of these cases was noted.

A group of patients in whom gross evidence of hepatic insufficiency and coma were noted were followed after institution of the hepatic regimen with the addition of intramuscular thioctic acid. In the majority of these a decrease in the elevations was noted and this decrease most often coincided with improvement in sensorium.

It is suggested that thioctic acid be added to the usual aggressive plan for the management of hepatic insufficiency and that further studies be planned to determine its essential role in the utilization of alpha-keto acids.

THE MECHANISM OF COPPER DEPOSITION IN THE LIVER IN HEPATOLENTICULAR DEGENERATION. *L. Lahut Uzman, Frank L. Iber, Marjorie Knowlton and Thomas C. Chalmers.* Walter Reed Army Medical Center, Washington, D. C.

Liver tissue was obtained surgically from a twelve year old asymptomatic boy who had hepatolenticular degeneration (HLD). The liver showed severe cirrhosis. A homogenate of the liver from this boy and one from the liver of a normal person were placed in cellophane tubing and dialyzed against buffered copper sulfate solution. Portions of the outside bath were removed for analysis, additional copper was added and the dialysis continued. The results revealed that the liver showing hepatolenticular degeneration bound from two to seven times as much copper with increasing copper concentrations as that of the liver from the normal person. An additional portion of the HLD liver homogenate and portions of two livers from normal persons were subjected to paper electrophoresis. The patterns were dried and stained for protein (ninhydrin) and copper (diethyldithiocarbamate). The HLD liver showed a high protein peak migrating slowly toward the anode that was entirely absent in the liver from the normal subject. This was called the X peak. Copper stains did not stain material in the liver from the normal subject but showed intense staining in the region of the X peak in the HLD liver. If the homogenates were treated with excess copper and then subjected to electrophoresis and stained for copper, marked activity was found in exactly the site of the X peak in the HLD liver. The studies thus demonstrate an increased affinity of the liver for ionic copper in Wilson's disease and that this increased affinity seems to be due to the high copper binding properties of an electrophoretically distinct protein present in the liver in Wilson's disease.

AMMONIA METABOLISM IN PATIENTS WITH CIRRHOSIS WHO HAD PORTACAVAL SHUNTS. *William W. Faloon, J. Howland Auchincloss, Robert Eich and Robert Gilbert.* State Univ. of New York, Upstate Medical Center, Syracuse, N. Y.

The association of portacaval shunt surgery with the occurrence of episodic stupor has

stimulated a study of blood ammonia in three patients with cirrhosis who had portacaval shunts. One, who had episodic coma, was studied while in deep stupor; another rapidly developed stupor when subsequently given ammonium chloride. Similar studies have been carried out in three patients with cardiac disease who did not have cirrhosis.

By venous catheterization blood NH_3 levels were determined in (1) inferior vena cava below the renal veins, (2) inferior vena cava above the renal veins, (3) inferior vena cava above the level of the shunt, (4) hepatic vein and (5) right auricle. Arterial blood NH_3 was determined simultaneously with most venous specimens. The highest elevations in blood NH_3 were found in the inferior vena cava above the shunt in patients with cirrhosis, representing a marked rise over that found in other locations. Hepatic vein NH_3 was normal in each patient. A rise in blood NH_3 above the renal veins occurred in all except one patient. Venous NH_3 was lower than arterial NH_3 in all instances in patients with cirrhosis except at the inferior vena cava above the shunt and above the renal veins. No significant A-V difference was observed in two of the three patients who did not have cirrhosis except in the hepatic vein, although one patient with previous severe cardiac decompensation had elevated blood NH_3.

The data indicate that defective extraction of NH_3 by the liver is of less significance than the shunting of blood around the liver in the production of elevated NH_3 levels in persons who had cirrhosis with portacaval shunts and that in persons who have cirrhosis with elevated blood NH_3 removal or binding of NH_3 by peripheral tissues occurs. These studies also suggest that administration of ammonium salts and institution of high protein diets may be more hazardous in the person who has cirrhosis with a shunt than in the patient upon whom no surgery was performed. The procedure used may also be of value in demonstrating the patency of a shunt postoperatively.

CHRONIC PORTAL-SYSTEMIC ENCEPHALOPATHY. *W. H. J. Summerskill, Sheila Sherlock and E. Davidson.* Postgraduate Medical School of London, London, England.

The characteristic neurologic features of hepatic coma were found present as a chronic neuropsychiatric disorder in fifteen patients with non-alcoholic cirrhosis of the liver. Fluctuating mental disorder with confusion, disorientation, bizarre behaviour and recurrent coma were associated with objective signs of which "flapping" tremor, hyperreflexia and limb rigidity were the most frequent. Electroencephalograms were similar to those described in hepatic coma.

Nervous disorder, often of several years duration, dominated the clinical picture and some patients had been committed to mental institutions. No patient had jaundice, and other evidence of disease of the liver was often scanty on physical or biochemical examination, although cirrhosis was invariably present on biopsy. Transplenic portal venography revealed extensive portal collateral circulation in every patient. The entire portal blood flow was diverted to the systemic circulation by portal vein thrombosis (five patients) or patent portocaval anastomosis (four patients), while a similar effect was due to enormously dilated patent umbilical veins in two other patients. Extensive collateral circulation in the absence of a single major channel was present in the remaining patients.

The neuropsychiatric disorder was shown to be due to intolerance of nitrogenous substances in the presence of a large collateral circulation and gross exacerbations could be provoked by high protein diet, ammonium chloride or methionine. Restriction of protein intake to 60 to 40 gm. daily resulted in restoration of intellectual powers and abolition of the neurologic abnormalities. The dramatic effect of treatment was demonstrated with a film. Follow-up studies over one to two years revealed no adverse effect of protein restriction.

DUBIN-JOHNSON SYNDROME IN ELDERLY MEN: REPORT OF THREE CASES. *Malcolm Campbell, C. P. Kolars, John I. Coe and F. W. Hoffbauer.* Univ. of Minnesota Medical School, Minneapolis, Minn.

Two men, aged seventy-two and seventy-six years, have been studied at the Minneapolis General Hospital; a third patient, aged sixty-eight, was studied at the University of Minnesota Hospitals. All three patients gave a lifelong history of asymptomatic jaundice. Surgical biopsy specimen secured in each instance demonstrated pigment in the hepatic parenchymal cells of the type described by Dubin and Johnson (*Medicine*, 33: 155–197, 1954). The serum bilirubin at the time of these observations was

distinctly elevated in each person (one minute values, 5 to 8 mg.; total, 9 to 15 mg. per 100 ml.). Non-visualization of the gallbladder by cholecystography and abnormal retention of bromsulphalein was demonstrated in two patients. At laparotomy a patent biliary tract and a normal gallbladder was noted in each instance. On inspection the liver presented a greenish-black color in each instance. One patient, aged seventy-six years, died as a result of arteriosclerotic disease of the heart and pneumonia. Autopsy confirmed the surgical findings as to the normal character of the biliary duct system and the hepatic discoloration.

These observations confirm the belief that the syndrome described by Dubin and Johnson is compatible with long life and does not appear to represent a progressive form of disease of the liver. (More detailed studies of these cases are to be presented elsewhere.)

THE PLACE OF BAL IN THE THERAPY OF WILSON'S DISEASE. *A. G. Bearn.* Rockefeller Inst. for Medical Research, New York, N. Y.

Despite the early successes of Denny-Brown in the use of BAL (2,3-dimercaptopropanol) for the treatment of Wilson's disease, its value as an effective therapeutic agent in this disease has been frequently questioned. In the last analysis, the rationale of BAL therapy must rest upon its ability to achieve and maintain an over-all negative copper balance before irreversible and destructive lesions of the brain have supervened.

The collection of a large number of patients with Wilson's disease made it possible to reassess the usefulness of this drug. It was found that patients could be divided into two main groups, those who regularly responded clinically to the drug (BAL-sensitive) and those who showed no such response (BAL-insensitive). The patients in the first category were frequently long-standing sufferers of the disease, particularly of the "pseudo-sclerotic" variety, whereas those who showed no response usually had one of the more acute forms. BAL was administered in larger doses than is conventionally advocated; 200 to 300 mg. BAL in oil was given twice daily for many months. Some patients have now been on almost uninterrupted therapy for over a year with striking and continued improvement. In an effort to diminish the intake of copper all patients were given a low copper diet (<1.8 mg. daily) as soon as the disease was recognized. In some instances carbo resin or sulphide was also administered orally. In some patients occasional severe "toxic" reactions to BAL were observed and somewhat limited the use of the drug. These reactions, which were not dependent upon the size of the dose, included high fever, gross increase in the neurologic signs already present, hallucinations, muttering delirium, temporary maniacal behaviour and even coma. However, in those few but fortunate patients in whom BAL appears beneficial, it would seem important to continue treatment indefinitely until better therapeutic agents become available.

RADIOACTIVE I-131 ROSE BENGAL UPTAKE AND EXCRETION TEST FOR LIVER FUNCTION. *Charles H. Brown and Otto Glasser.* The Cleveland Clinic Foundation and The Frank E. Bunts Educational Inst., Cleveland, Ohio.

Taplin, Meredith and Kade (*J. Lab. & Clin. Med.*, 45: 665–678, 1955) obtained liver "uptake" and "excretion" curves by giving radioactive rose bengal solution and then directing a gamma ray counter over the liver. In normal rabbits a rapid and high uptake was followed by rapid excretion. The uptake in rabbits twenty-four hours after carbon tetrachloride poisoning was not as high or as rapid, and excretion was much slower. In rabbits with common duct ligation there was rapid and high uptake but no excretion. Decreased but more prolonged uptake and delayed excretion was found in patients with disease of the liver.

Eighty patients were studied using the radioactive (I-131 tagged) rose bengal test, the solution being given intravenously, and a scintillation counter with a small diaphragm pointed over the liver subsequently for seventy-five minutes. The time required for the peak uptake was delayed in most patients with disease of the liver and also in patients with obstructive jaundice. The mean height of the uptake was lower in these patients than in the normal patients. Excretion of radioactive material from the liver was delayed in patients with disease of the liver and obstructive jaundice. Typical normal tracings show rapid uptake to a high level with the excretion starting in thirty to forty minutes. Curves for patients with disease of the liver (Laennec's cirrhosis, hepatitis, postnecrotic cirrhosis and chlorpromazine hepatitis) demonstrate delayed, prolonged and low uptake and delayed excretion. Changes in the curves, similar to those obtained in patients with

Laennec's cirrhosis, were obtained in patients with proved obstructive jaundice. One patient with a large hepatoma showed very little uptake over the tumor.

This test demonstrates abnormal changes in patients with disease of the liver but, as used, did not differentiate hepatic from obstructive jaundice. Refinements of this test and further studies with radioactive material may be of considerable help in understanding the physiology of the liver and may be of value clinically.

CLINICAL AND LABORATORY STUDIES OF AN EPIDEMIC OF INFECTIOUS HEPATITIS IN CALLOWAY COUNTY, KENTUCKY. *I. A. Schafer, H. F. Eichenwald, J. W. Mosely, J. I. Karush, T. A. Asher, M. L. Candler and G. R. Cooper.* Communicable Disease Center, U. S. Public Health Service, Atlanta, Ga.

An epidemic of infectious hepatitis in Calloway County, Kentucky, was studied during the summer and fall of 1954. The peak of the epidemic occurred in August 1954, after a slow spread had occurred through the community. The rate of attack for all the age groups up to age fifty was similar. No differences were noted in the ratio of icteric to non-icteric cases regarding age or sex. Because the rate of attack was unusually similar in all age groups, it was believed that the subjects had not been previously exposed and therefore were susceptible.

Sixteen per cent of persons coming into contact with the family acquired the disease. Use of gamma globulin produced a marked reduction in the rate of severity of secondary attacks. Person to person transmission appeared to be the principal method. The patients had jaundice and/or enlarged and tender liver, or abnormal liver function reactions with compatible clinical and epidemiologic histories. Clinically the cases showed a high incidence of lassitude, abdominal discomfort, anorexia, nausea, fever, headache and myalgia. Two liver biopsy specimens and one autopsy revealed findings compatible with viral hepatitis. Serologic tests for heterophil and leptospiral antibodies gave negative results.

Follow-up studies were conducted one year later on the patients and their contacts, who were seen during the original epidemic, to determine if any effects were persistent. On re-examination 50 per cent of the cases showed physical abnormality with and without concurrent clinical symptoms. Particularly striking were the complaints of menstrual difficulties, loss of normal hair curl and loss of normal hair texture among young women. Fatigue, loss of libido and personality changes were frequent complaints among the adults. In 35 per cent of the patients laboratory data gave abnormal results. The gamma content of the serum determined by paper electrophoresis and zinc sulfate turbidity test correlated best with the clinical history and physical examination. A few patients with persistent splenomegaly did not show evidence on peripheral blood smears of hematologic disease.

CONGENITAL NON-HEMOLYTIC NON-OBSTRUCTIVE JAUNDICE WITH DISEASE OF THE CENTRAL NERVOUS SYSTEM. *Ira M. Rosenthal and Hyman J. Zimmerman.* West Side V. A. Hosp., Chicago, Ill.

The case of a six year old boy with congenital non-hemolytic non-obstructive jaundice associated with central nervous system disease is reported. The child had a marked elevation of serum bilirubin (20 mg. to 100 cc.), practically all of which was in the indirect phase. Only minor abnormalities were found in a section of liver obtained at laparotomy. Neurologic symptoms began at the age of three years. This patient appeared to suffer from a disease first described by Crigler and Najjar in 1951 under the name "familial non-hemolytic jaundice with kernicterus." None of their patients, however, followed the course observed in this child. The pathogenesis and differential diagnosis of this disease are discussed.

EXPERIENCES WITH THE DIAGNOSIS OF MALIGNANT LESIONS OF THE LIVER BY NEEDLE BIOPSY. *Maurice H. Stauffer, William T. Foulk, John B. Gross and Malcolm B. Dockerty.* Mayo Clinic, Rochester, Minn.

In the experience of the authors, one of the most important uses for needle biopsy of the liver has been in the diagnosis of primary or metastatic malignant lesions. Between 1948 and 1954 at the Mayo Clinic 850 needle biopsies were performed. In this series 243 biopsy specimens revealed microscopic evidence of malignant lesions. In another forty-six cases it was considered that the neoplasm had been missed because of subsequent surgical biopsy, necropsy, repeat needle biopsy or clinical findings. Concerning 161 patients a definite clinical impression of malignant disease of the liver was obtained and it might be considered confirmed by the biopsy. However, in sixty-seven cases in

which the clinical diagnosis was indeterminate a neoplasm was proved by biopsy of the liver. In another group of fifteen patients for whom a positive diagnosis of malignancy was made by this method a previous erroneous clinical diagnosis had been made.

The authors prefer the subcostal approach for biopsy when hepatomegaly is present and especially when palpable nodules are present. The transthoracic route was used in only nine instances in the group of 243 in which results of biopsy were positive. No fatalities resulted from the procedure in the group of patients with malignant disease of the liver; however, in the entire series of 850 cases, two deaths occurred from bile peritonitis in patients with extrahepatic obstructive jaundice.

In 103 instances more than one specimen was obtained, which materially enhanced the possibility of obtaining neoplastic tissue. In the other 140 cases the diagnosis was made on the basis of a single biopsy specimen. In 112 cases the tissue was prepared by the fresh-frozen section technic, and the pathologic interpretation was made within a few minutes.

Among the 289 patients with neoplastic disease of the liver, results of biopsy were positive in 83 per cent. On the basis of this study the authors have concluded that needle biopsy of the liver is an excellent method for establishing the diagnosis of malignant hepatic lesions.

MITOCHONDRIAL PHOSPHOLIPIDS IN CIRRHOSIS. *W. E. Cornatzer and D. G. Gallo.* Univ. of North Dakota Medical School, Grand Forks, N. D.

Phospholipid synthesis is a primary function of cell processes. Mitochondria and large granules are very rich in phospholipids. Male rats (100 to 110 gm.) were divided into three groups and maintained for four weeks on a stock diet (30 per cent protein) and on 25 and 5 per cent purified casein diets. The composition of total lipid, lecithin, sphingomyelin, and cephalin phospholipids was determined as homogenates and mitochondria preparations of the liver. A decrease occurred in the total lipid and lecithin phospholipids in the liver mitochondria of those animals maintained on a 5 per cent casein diet as compared to the stock diet or the 25 per cent casein one. Administration of a single dose of choline (40, 75 or 150 mg.) six hours before sacrificing the animals maintained on a 5 per cent casein diet produced a significant increase in lecithin phospholipid of the mitochondria. This effect of a single dose of choline (150 mg.) was demonstrated within three, six or ten hours following administration.

USEFULNESS OF SERUM TRANSAMINASE IN VARIOUS LIVER DISEASES. *David W. Molander.* New York Hosp., Cornell Univ. Medical School, New York, N. Y.

Serum glutamic oxalacetic transaminase was determined according to Karmen's method in a series of patients with various diseases of the liver. The normal range varied from 5 to 40 units per ml. serum. Patients with Laennec's cirrhosis were divided into two groups. In thirty-eight patients with compensated cirrhosis, the enzyme activity ranged from 13 to 150 units, with a mean of 45 units. In forty-three patients with decompensated cirrhosis the activity varied from 28 to 286 units, with a mean of 79 units. In seven patients with biliary cirrhosis twelve determinations ranged from 57 to 330 units. The mean was 160 units. Significant levels were seen in two patients during the fifth week of convalescence from hepatitis. In one recrudescence was predicted because of the increase of enzyme activity. In a patient with obstructive jaundice due to Hodgkin's disease that involved the common duct, the initial level was 320 units and after surgical relief of the obstruction the level fell to 27 units. A value of 1,248 units was obtained two days before death in one patient with acute decompensation of cirrhosis. Hepatitis was diagnosed sixty days following a postcaval shunt by a level of 2,870 units.

Elevated transaminase levels imply parenchymal liver cell necrosis. The sensitivity of the test imparts useful information to the clinician in the management of patients with disease of the liver.

SYNDROME OF CIRRHOSIS OF THE LIVER WITH NORMOCHOLESTEREMIC PULMONARY AND RHEUMATOID CHOLESTEROSIS. *Arthur L. Scherbel and Thomas E. Wilson.* Cleveland Clinic, Cleveland, Ohio.

A syndrome of cirrhosis of the liver, rheumatoid arthritis, pulmonary cholesterosis and normal serum cholesterol of long duration, has not been reported in the literature. A case with certain similarities except for hypercholesteremia and atherosclerosis which developed five years after onset of chronic polyarthritis was reported in 1939. Cholesterol has been

reported in rheumatoid nodules and has been considered a normal variation of rheumatoid arthritis.

A fifty-four year old white man was admitted to the hospital in 1955 for study and treatment because of severe crippling arthritis that had begun in 1939. The initial illness was sudden and was manifested by pericarditis, migratory polyarthritis and pleurisy. In 1949 examination revealed a right pleural effusion and multiple nodular densities throughout both lung fields. Thoracentesis revealed cloudy yellow fluid loaded with cholesterol crystals and fat globules. Cultures were negative for tubercle bacilli. The arthritis remained active and progressed to subluxation and ankylosis. Examination in 1955, in the seventeenth year of illness, revealed large yellow subconjunctival plaques, vitreous floaters and corneal opacities. The liver was palpated 4 cm. below the right costal margin, and marked palmar erythema was noted. The nodular densities throughout both lung fields were unchanged. Serum cholesterol has ranged between 117 and 170 mg. per cent since 1950. A liver biopsy specimen revealed mild cirrhosis compatible with the postnecrotic type. Fluid aspirated from the right knee joint contained many cholesterol crystals, and the cholesterol level of this fluid was 400 mg. per cent with cholesterol esters of 211 mg. per cent as compared with a simultaneous serum cholesterol of 130 mg. per cent. Synovial biopsy specimens of the right knee and wrist revealed marked cholesterosis. A rheumatoid nodule contained numerous cholesterol clefts.

Studies are contemplated in order to determine whether cholesterol is transported or formed *in situ* in joint and pleural spaces.

Case Reports

Chronic Idiopathic Jaundice*

Two Cases Occurring in Siblings, with Histochemical Studies

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FOLLOWING the establishment of familial hemolytic jaundice as a disease entity, it became apparent to Gilbert that a certain small percentage of patients included in this classification was significantly different in that hemolysis was not present to account for jaundice, obstruction of the bile ducts was not found and hepatocellular necrosis was excluded by histologic examination. The bilirubin was predominantly of the indirect variety. This entity was subsequently described by other investigators and designated physiologic hyperbilirubinemia, constitutional hepatic dysfunction and familial non-hemolytic jaundice. Rotor subsequently described a variant of familial non-hemolytic jaundice in which the bilirubin reaction was primarily direct and the liver biopsy specimen was normal on histologic examination.

In September, 1954, Dubin and Johnson described twelve cases of chronic idiopathic jaundice that, while similar to familial non-hemolytic jaundice, differed in two significant ways: first, the bilirubin reaction was primarily direct; second, the liver histology was essentially normal except for coarse brown centrolobular pigmentation.[1] In November, 1954, Sprinz and Nelson independently proposed the new disease entity of persistent non-hemolytic hyperbilirubinemia associated with lipochrome-like pigment in liver cells.[2] They reported four cases; their conclusions were quite similar to those of Dubin and Johnson. Up to the present time there have been twenty-one cases collected by the Armed Forces Institute of Pathology;[3] while three of these patients had a definite history of familial jaundice, the existence of this syndrome in blood relatives has never been proved.

The purpose of this paper is to present two cases in a brother and sister that satisfy the requirements of Dubin and Johnson for chronic idiopathic jaundice.

CASE REPORTS

CASE 1. E. J. O. (No. 15189) was well until the age of nineteen when, exposed to the rigorous stresses of armed combat in January, 1945, he experienced sudden onset of weakness and fatigue. During the following week dark urine, anorexia, soreness in the right upper abdominal quadrant and light-colored diarrhea developed. He was noted to have jaundice and was evacuated to England where the diagnosis of acute and chronic hepatitis was made. Treatment consisted of bedrest and a high caloric, low fat diet. These measures were continued for the remainder of his nine months of hospitalization. During this period the jaundice fluctuated in intensity, was ordinarily accompanied by soreness in the right upper abdominal quadrant and was thought to be precipitated by activity. Icterus indices ranged from 10 to 24 but the serum proteins, hippuric acid test and erythrocytic osmotic fragility tests were normal. An oral cholecystogram demonstrated faint visualization of the gallbladder. In April, 1945, the patient was transferred to the United States where hospitalization was continued until October. During this period, bromsulfalein retention ranged from 4 to 28 per cent (normal less than 10 per cent). Bilirubin was occasionally present in the urine. Urine urobilinogen was never elevated (Wallace and Diamond method). The patient was discharged from military service with a diagnosis of "chronic infectious hepatitis, unimproved by hospitalization."

Since that time he has suffered frequent recurrence of soreness in the right upper abdominal quadrant, fatigue and jaundice. These episodes occurred about twelve times a year, two or three each year being more severe and associated with light-colored diarrhea and dark urine; they sometimes followed unusual

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activity. Laboratory tests recorded during reinvestigation at Crile Veterans Administration Hospital in June, 1947, included a normal blood cholesterol and bromsulphalein reaction but positive thymol turbidity reaction and increased serum total bilirubin.

The most recent episode began on December 22, 1954. It was initiated a few minutes after ingesting candy, and consisted of a severe, steady, non-radiating epigastric pain, disappearing during the next two days except for a residual ache in the right upper quadrant. The more severe pain recurred after a lapse of two days but lasted only two hours. Jaundice increased and the patient noted light-colored diarrhea and dark urine, without chills and fever.

Review of the family history disclosed that he had an older sister who had recurring jaundice since the age of twelve years. Review of the past history revealed minimal alcoholic consumption and no exposure to hepatotoxins.

Physical examination when admitted to Seattle Veterans Administration Hospital on January 26, 1955, showed a well developed, well nourished twenty-nine year old white man with moderate skin and scleral icterus and tenderness to percussion over the liver area anteriorly. Cephalin flocculation test, prothrombin time, thymol turbidity, alkaline phosphatase, BSP retention (5 mg./kg. in forty-five minutes), serum proteins (including paper electrophoresis), urine urobilinogen, serum amylase and cholesterol were all normal. Bilirubin was present in the urine, the serum bilirubin (method of Evelyn and Malloy) being 2.0 mg. per cent direct and 4.2 mg. per cent total. The cholecystogram following double the usual dose of telepaque showed faint visualization of the gallbladder.

All observers believed that the patient probably had obstruction of the biliary tree but many remarked on the somewhat atypical laboratory findings of the case. Accordingly, the patient was subjected to abdominal exploration on February 9, 1955. The liver was found to be mildly enlarged and purplish blue in color. The gallbladder, bile ducts and pancreas were normal. A wedge biopsy specimen of the liver was removed. The postoperative course was uneventful and the patient was discharged on February 24, 1955. He returned to work, but jaundice was still present.

Case II. E. O. W. (the sister of the patient in Case I) was the subject of a previous report dealing with infectious hepatitis and its effects upon the fetus when occurring in the first trimester of pregnancy.[4] Her first episode of jaundice occurred at age twelve, confining her to bed for one month and leaving her weak for the following year and in an icteric state thereafter. She had frequent pain in the right side of the abdomen associated with deepening of the scleral icterus and onset of noticeable skin jaundice. At age twenty she was delivered of her first normal child, but her next two pregnancies terminated in spontaneous abortion. Jaundice became very severe during the eighth month of the fourth pregnancy and the patient was delivered of a premature infant. The fifth and sixth pregnancies also terminated in spontaneous abortion with curettage. A 1,000 cc. whole blood transfusion was necessary after the fifth pregnancy.

In June, 1949, the patient again experienced severe jaundice, intense pain on the right side of the abdomen and fatigue which prompted her to seek medical attention. At this time the cephalin flocculation test was 2-plus, the urine urobilinogen reaction negative, the prothrombin time 100 per cent and the serum bilirubin 6.9 mg. per cent direct and 9.1 mg. per cent indirect. A presumptive diagnosis of infectious hepatitis was made and the patient was treated with rest, high protein, high carbohydrate, low fat diet and vitamins. One month later she again became pregnant. Cholecystography disclosed a non-functioning organ without evidence of stones. Watchful waiting was elected in favor of therapeutic abortion. Clinically, she improved until the sixth month of gestation when a streptococcal pharyngitis occurred following which clinical deterioration was noted, and she was given additional protein supplements. Near the end of pregnancy she was hospitalized for induction of labor. The serum bilirubin was 5.6 mg. per cent direct and 6.9 mg. per cent indirect, the cephalin flocculation test 3-plus, the thymol turbidity test 13.2 the alkaline phosphatase 2.2 and a normal erythrocytic osmotic fragility reaction. Labor was induced and the patient was delivered of a composite monster.

The postpartum course was uneventful and in one month she was subjected to abdominal exploration. The liver was dark green to black; the gallbladder was filled with pigment-cholesterol stones. Cholecystectomy and bilateral tubal ligation were performed and a liver biopsy specimen was removed. In the five years since the operation the patient has continued to have an icterus index of from 24 to 28[5] but believes that she has improved in strength and recuperative power, and has gained weight. She reports that she is still susceptible to intestinal "flu" but now at the age of thirty-four is in good physical condition.

Two other sisters, both in the late twenties, are reported to have had several attacks of "gallbladder trouble" in the past year but are as yet uninvestigated.

PATHOLOGIC DATA

Grossly the wedge biopsy specimen of the liver in Case I revealed a smooth, thin capsule with dark green, discolored liver tissue. Microscopically multiple sections stained with hematoxylin and eosin revealed the lobular architecture to be intact. In the centrolobular zone there was a striking deposition of coarsely granular brown pigment within the cytoplasm of the liver cells. (Fig. 1.) This amorphous pigment tended to be most prominent around the central vein with

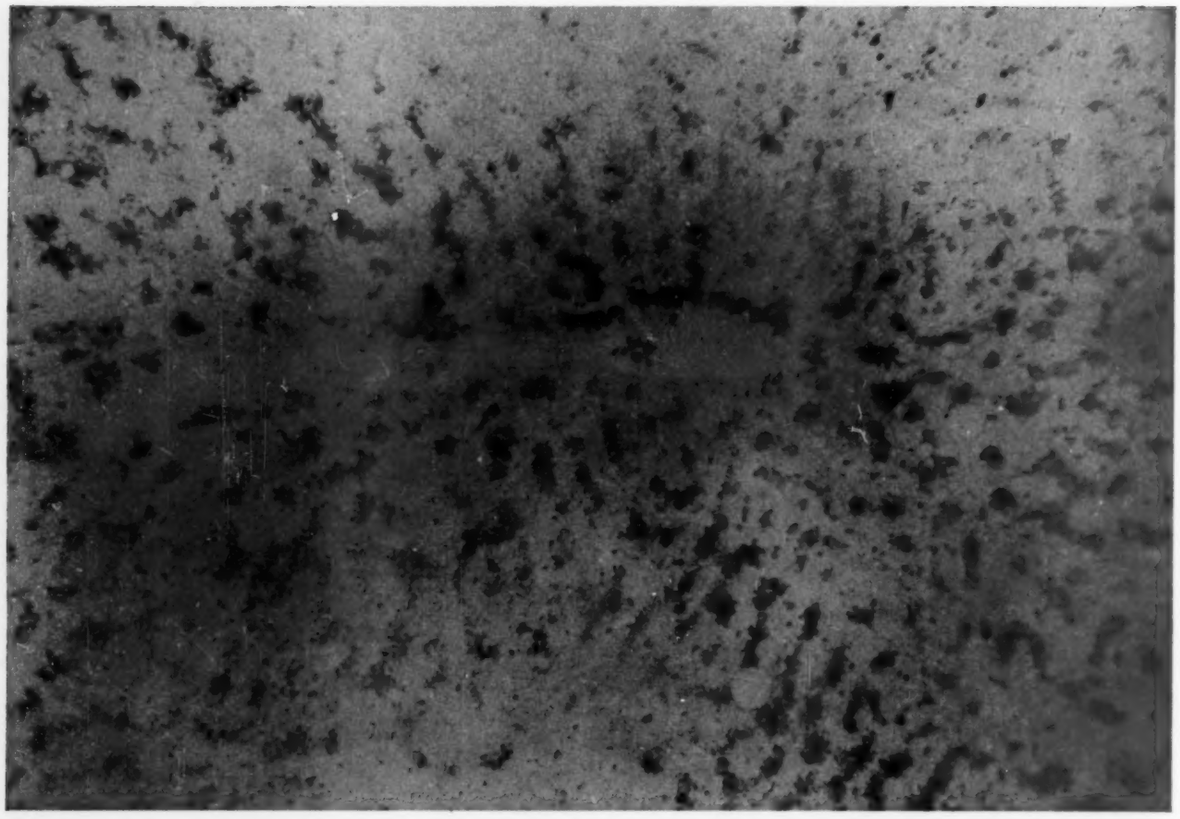

FIG. 1. Case I. Unstained section showing centralobular pigmentation of liver cells; original magnification × 100.

scattered diffuse pigment at the periphery of the lobule. The von Kupffer cells were essentially free of pigment. The periportal areas revealed well defined ducts with only occasional mononuclear cells present. The bile canaliculi were entirely free of bile thrombi.

Histochemically frozen section on fresh tissue stained with oil red 0 showed a strong affinity of the pigment for the fat stain. The granules gave a negative reaction for hemosiderin pigment. The granules were strongly positive after treatment with periodic acid-Schiff reagent with digestion and also reacted to a certain extent with Mallory's basic fuchsin stain. The Gomori iron stain gave a negative reaction as did the Stein test for bilirubin. Sections mounted in glycerin for polarization microscopy revealed isotropic granules.

Grossly the wedge biopsy specimen of the liver in Case II was dark green in color. The surface of the capsule was smooth. Microscopically section of the liver biopsy specimen (Case II) revealed histologic changes identical with those noted in Case I. (Fig. 2.) The coarse granular pigmentation of the centrolobular area was prominent.

COMMENT

Chronic idiopathic jaundice with unidentified pigment in the liver cells was first proposed as a clinical entity separate from all other known causes of jaundice but closely related to constitutional hyperbilirubinemia (Gilbert's disease) by Dubin and Johnson in September, 1954, at which time they reported twelve cases which qualified for this entity. Sprinz and Nelson independently described the same entity in Novemver, 1954, and reported four cases.

The clinical syndrome consists of continuing low grade or recurring icterus, fatigue, malaise and abdominal pain, with exacerbations probably occurring as a result of infection or other stress. Liver function studies of the other cases reported have usually showed marked variation in the flocculation tests and elevated BSP retention, with bilirubinuria and an elevated serum bilirubin of which at least 50 per cent was of the direct reacting type. The liver was found to be

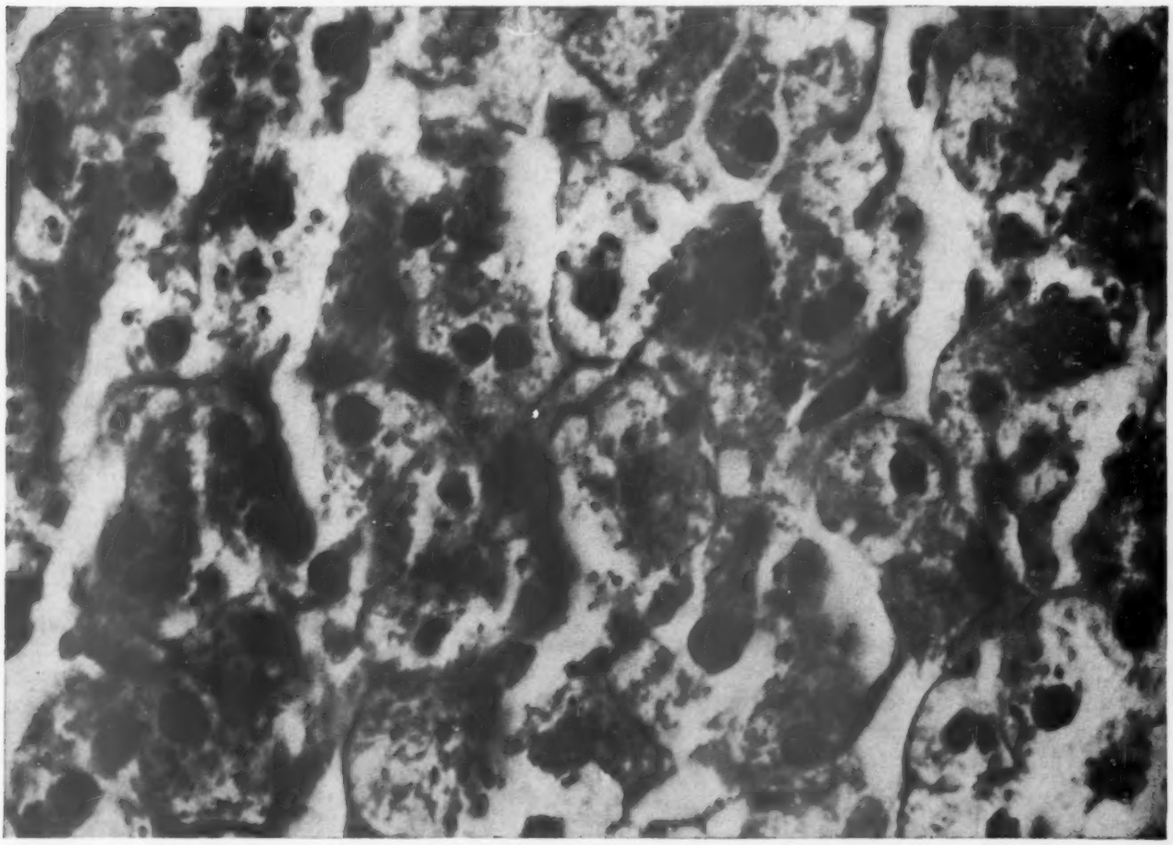

FIG. 2. Case II. Section of liver stained with hematoxylin and eosin showing granular pigmentation of liver cells; original magnification × 350.

quite dark in color and histologically displayed coarse brown granular pigment most heavily concentrated in the centrolobular area.

The exact etiology of this disease is unknown but it has been thought to be an inborn or acquired error of metabolism in consequence of which the liver cannot adequately excrete the substance responsible for the liver pigmentation, bilirubin, bromsulphalein, and the dyes used for cholecystography. Recognition of the syndrome and its excellent prognosis obviates the stigma of the diagnosis of chronic infectious hepatitis, and avoids unnecessary surgery. Histologic examination of the liver specimen is essential in establishing the diagnosis. A family history was strongly suggested in several of the previous case reports but proof of its existence in blood relatives had never been established before.

Case I presented a fairly typical history for the syndrome with onset similar to infectious hepatitis and continuation in chronic form for the next ten years. The clinical history, physical examination and laboratory data pointed to biliary obstruction with some atypical laboratory findings, and eventually culminated in surgical exploration. One of the most impressive laboratory findings was that of 1 per cent BSP retention in the face of a moderately elevated direct serum bilirubin. Case II either had or was thought to have had infectious hepatitis at age twelve since which time she had noted recurrent attacks of jaundice. She was thought to have had a recurrence of infectious hepatitis just prior to her final pregnancy, but the clinical status improved during pregnancy until a difficulty controlled streptococcal pharyngitis developed. The patient eventually was delivered of a monster, a circumstance attributed to the presence of a virus infection (hepatitis) during the first three months of pregnancy. The liver architecture one month after delivery disclosed only coarse brown centrolobular pigmentation and showed none of the fibrosis or inflammatory change that might be expected from long-standing viral

hepatitis. The monster may well have been coincidental and not the result of viral infection in the first trimester of pregnancy.

It is also of interest that the gallbladder contained 300 odd pigment cholesterol stones. This again may well have been coincidental and occurred as a process separate from the chronic idiopathic jaundice but nevertheless serves to point out that biliary tree disease may be expected in this syndrome, and may indeed present a confusing picture.

The possibility that more than just these two siblings have this disease entity is likely in that two other relatively young sisters have had attacks of "gallbladder trouble."

The striking pigmentation of the liver both on gross and microscopic examination in our cases fits well into the entity of chronic idiopathic jaundice described by Dubin and Johnson. The prominent affinity of the granules for oil red 0 on frozen section together with the other histochemical properties previously described suggests that the pigment may be related to the lipochrome group. The strong affinity for oil red 0 in our case may be accounted for by the opportunity to use fresh tissue for the frozen sections.

SUMMARY

Two cases in siblings which satisfy the requirements of Dubin and Johnson for chronic idiopathic jaundice are presented. The familial nature of the disease had been suspected but not heretofore proved.

The etiology of the syndrome is still doubtful but appears to be a selective inability of the liver to excrete certain substances.

The identity of the coarse brown centrolobular pigment is still in question. The availability of fresh liver tissue has added a strongly positive oil red 0 reaction to those histochemical reactions previously obtained.

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REFERENCES

1. Dubin, I. N. and Johnson, F. B. Chronic idiopathic jaundice with unidentified pigment in liver cells. *Medicine*, 33: 155, 1954.
2. Sprinz, H. and Nelson, R. S. Persistent non-hemolytic hyperbilirubinemia associated with lipochrome-like pigment in liver cells. *Ann. Int. Med.*, 41: 952, 1954.
3. Personal communication.
4. Kellogg, C. S. and Wesp, J. E. Infectious hepatitis during pregnancy and its effect upon the fetus. *Am. J. Obst. & Gynec.*, 62: 1153, 1951.
5. Kellogg, C. S. Personal communication.

Coexisting Histoplasmosis and Tuberculosis of the Alimentary Tract*

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Concurrent infection by both Histoplasma capsulatum and Mycobacterium tuberculosis results in an intriguing combination of diseases which has generally been regarded as something of a medical curiosity because of its assumed rarity. However, judging from the 10 per cent incidence of tuberculosis among 138 cases of histoplasmosis reported prior to 1950,[1] this does not appear to be as unusual an association as has been generally supposed. In fact, additional instances of dual infection have been recognized with increasing frequency,[2–10] and a recent discussion of the subject[11] indicates its growing importance. This article, while prompted primarily by the occurrence of these two diseases in one patient, contains other unusual aspects, not the least of which is the possibility that the patient contracted histoplasmosis while in the hospital where he had been confined for the treatment of tuberculosis during the preceding twenty-one months.

CASE REPORT

E. M., a fifty-nine year old white bartender, was admitted to the hospital on March 29, 1950, complaining of swelling of his feet and ankles and weakness of his legs of one month's duration. Except for excessive alcoholic ingestion his past history had not been remarkable and the patient considered himself in good health until one year prior to admission. At that time a chronic productive cough developed associated with progressive weight loss which eventually amounted to approximately thirty pounds. In spite of these symptoms he remained active until one month before admission, when he first noticed the onset of pedal edema. Ulcers soon developed over the lower third of each leg; and because of increasing weakness of his lower extremities he was finally unable to walk and sought hospitalization.

Physical examination disclosed a debilitated, somewhat emaciated white man, who appeared chronically ill. Personal hygiene was very poor but the patient was rational, fairly intelligent and cooperative. He weighed 121 pounds. Temperature, pulse and blood pressure were normal. Dental hygiene had been neglected and the teeth were in a state of poor repair. The scleras had a slight icteric tinge. The chest was barrel-shaped and crepitant rales were heard over both pulmonary apices. Resonance was impaired over the left mid-lung field posteriorly. The liver edge was palpable on deep inspiration about three finger-breadths below the right costal margin; the edge was firm, somewhat irregular and non-tender. There was four-plus pitting edema of both lower extremities with huge areas of reddish black discoloration and superficial ulcerations over the skin of the lower legs. Several toes were also discolored. The dorsalis pedis and popliteal pulsations were palpable bilaterally but the posterior tibial pulsations could not be detected. Cyanosis of the hands and nail beds was present and there was slight clubbing of the fingers. The remainder of the physical examination was within normal limits.

Roentgenogram of the chest on admission (Fig. 1) disclosed diffuse patchy densities throughout the upper three-fourths of both lung fields. The infiltration was most confluent in the upper portions of the left lung, and in this area there were multiple circular lucencies which strongly suggested the presence of cavitation. Sputum was repeatedly positive for tubercle bacilli by both concentrate and culture. Blood count was within normal limits. Sedimentation rate was 33 mm. in one hour (Westergren). Urinalysis disclosed no abnormality. A serologic test for syphilis gave positive results (64 Kahn units). Serum protein was 5.1 gm. per cent; albumin 3.2 gm. per cent; globulin 1.9 gm. per cent. Total serum bilirubin was 1.25 mg. per cent. Two-hour urine urobilinogen was 3 Ehrlich units. Cultures taken from the ulcerations on the lower extremities showed hemolytic staphylococcus aureus. The remainder of the initial laboratory examinations, including liver function studies, electrocardiogram and spinal fluid examination, were within normal limits.

A diagnosis of far advanced active pulmonary tuberculosis was established. In addition, it was believed that the patient was suffering from the effects of severe malnutrition, chronic alcoholism and very poor personal hygiene, which were manifested in the

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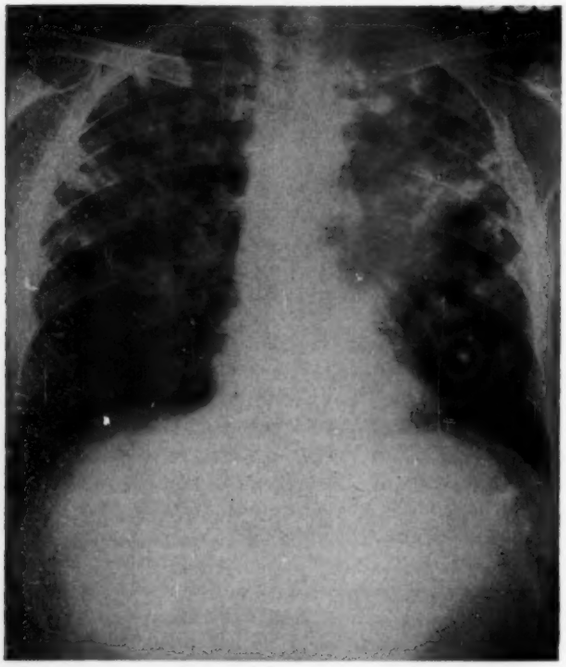

FIG. 1. Roentgenogram of the chest at the time of admission (March 29, 1950).

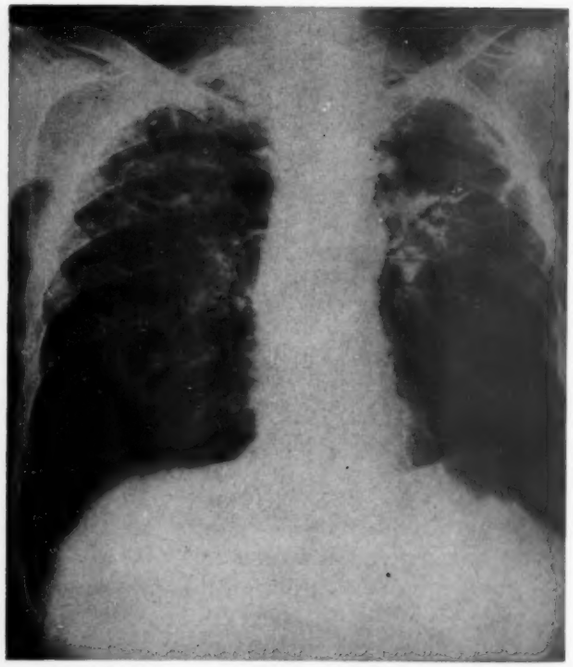

FIG. 2. Roentgenogram of the chest (January 16, 1952) taken twenty-two months after admission, one month after the diagnosis of oral histoplasmosis was established and three weeks prior to death. This x-ray illustrates maximum regression of the pulmonary lesions.

form of nutritional edema and probably fatty infiltration of the liver. He was placed on complete bedrest. Local treatment of the superficial ulcerations of the lower extremities was promptly instituted, with good results. Supportive therapy directed at correction of malnutrition and probable liver disease was carried out concomitantly along with an intensive course of penicillin as an antiluetic measure. Dihydrostreptomycin, 1 gm. daily, was started as soon as the sputum was found to contain acid-fast bacilli.

Under the foregoing management the patient exhibited gradual clinical improvement. He soon became afebrile; his pedal edema quickly resolved; the liver became impalpable; weight and appetite improved; and serology converted to negative. However, following administration of 120 gm. of streptomycin there had been only minimal improvement in the bilateral pulmonary lesions and sputum continued to contain acid-fast bacilli. Pneumoperitoneum was therefore induced on October 14, 1950, after surgical repair of the patient's bilateral inguinal hernias had been carried out. On this therapy further regression of the exudative components of the pulmonary lesions occurred but large cavities appeared in the upper portions of both lung fields and tubercle were still present in the sputum. On June 6, 1951, pneumoperitoneum was abandoned because of recurrence of a left inguinal hernia. Shortly thereafter a low grade fever developed and the patient gradually lost weight. A second course of streptomycin was started on September 14th.

No significant change in the patient's general clinical condition took place until December 17th when a large ulcerating lesion was discovered on the right posterosuperior portion of the tongue (Fig. 3), previous knowledge of which the patient emphatically denied. There was no associated lymphadenopathy. Biopsy of the lesion revealed numerous histoplasma in a stained impression and also in tissue sections. (Fig. 4.) H. capsulatum was isolated in repeated cultures. (Fig. 5.) At this point the clinical course was downhill and the patient started to complain of marked anorexia and occasional nausea and vomiting. His weight declined steadily and intermittent temperature elevations were somewhat higher than before. The local ulceration on the tongue was treated with saline mouth washes, with rapid and apparently complete healing within two to three weeks. Roentgenogram of the chest disclosed no evidence of progression of the pulmonary lesions. (Fig. 2.) When cultures of blood, bone marrow and sputum were negative for fungi, it was hoped that the oral lesion represented the only focus of mycotic disease but liver biopsy disclosed a single small granuloma compatible with histoplasmosis. (Fig. 6.) Although this lesion could not be distinguished from a tuberculous granuloma, a presumptive diagnosis of disseminated histoplasmosis was then considered.

On February 2, 1952, the patient complained of mild abdominal cramps associated with nausea and vomiting. Physical examination at this time dis-

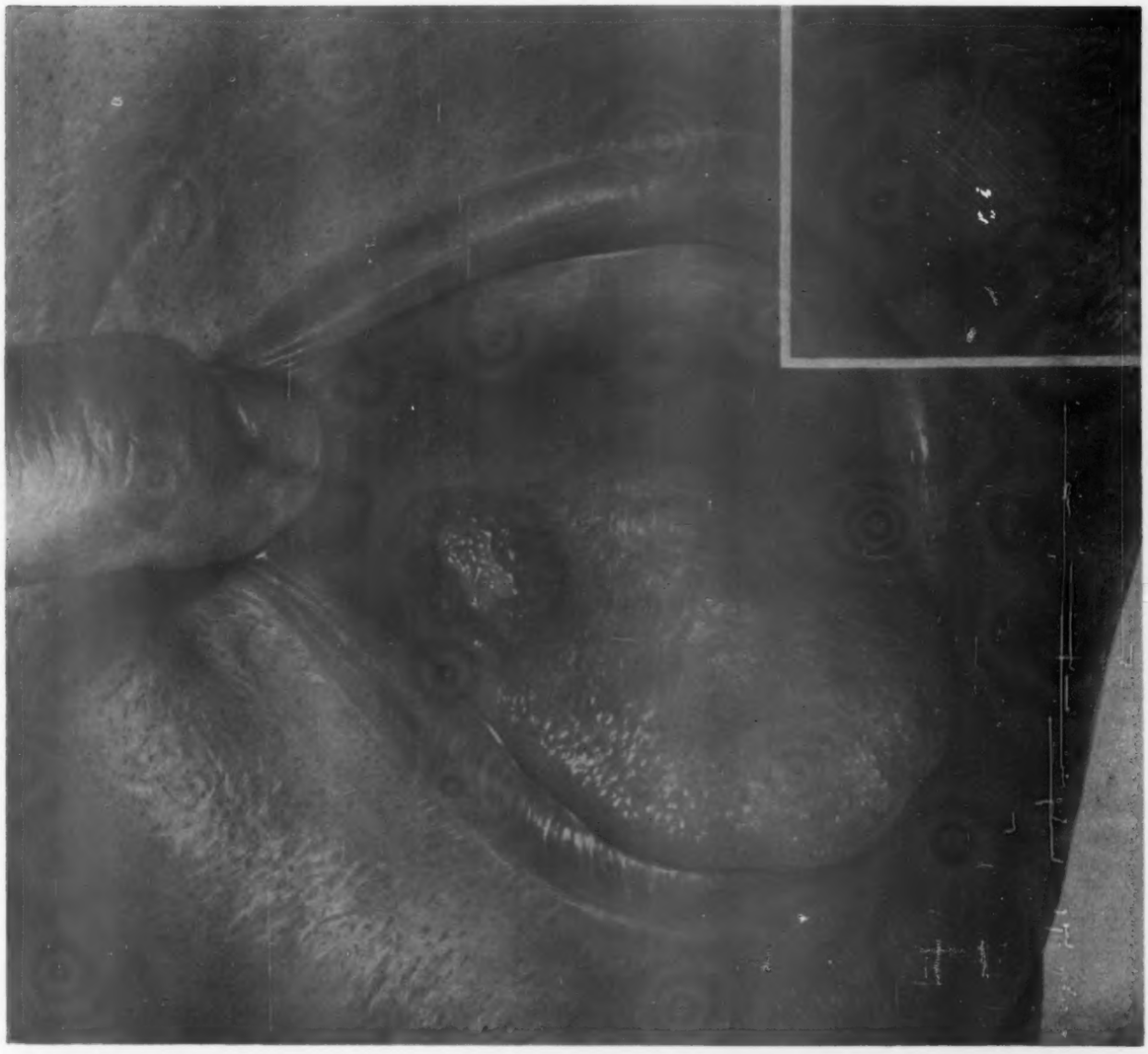

FIG. 3. Sketch of patient's tongue showing a large ulcer which contained Histoplasma capsulatum. Insert illustrates appearance of the ulcer after healing had taken place.

closed generalized abdominal tenderness and rigidity. Thereafter his condition deteriorated rapidly; however, he had no further complaints and steadfastly insisted that he "felt fine," although by this time he was markedly emaciated, was too weak to sit up, and refused everything by mouth except water. It was postulated that peritonitis had developed secondary to perforation of an ulcer caused by histoplasmosis in the gastrointestinal tract. Because of his extremely poor clinical condition and presumably hopeless underlying disease, laparotomy was not performed but promin® therapy was instituted. The patient continued to do poorly, soon became semi-stuporous, and expired quietly on February 8th. The clinical diagnoses were chronic far advanced pulmonary tuberculosis and disseminated histoplasmosis with peritonitis from a perforated enteric ulceration.

At autopsy an indurated area was present along the right posterolateral margin of the tongue. (Insert, Fig. 3.) There was no residual ulceration. The peritoneal cavity contained 1,500 cc. of foul, feculent pus. A perforation was found in the distal ileum 5 cm. proximal to the ileocecal valve. The left pleural space contained 500 cc. of dark brown fluid. This loculus was continuous with a similar accumulation in the lower mediastinum, the two being connected by a rent in the mediastinal pleura. A small perforation of the esophagus was demonstrated 4 cm. above the cardia. (Fig. 7.)

Externally the lungs presented many fibrous adhesions. By palpation both lungs contained many nodules. On cut surface a huge cavity in the right apex was found to measure 7 cm. in diameter; it contained a large amount of creamy material. In the left lung several smaller cavities, approximately 1 cm,.

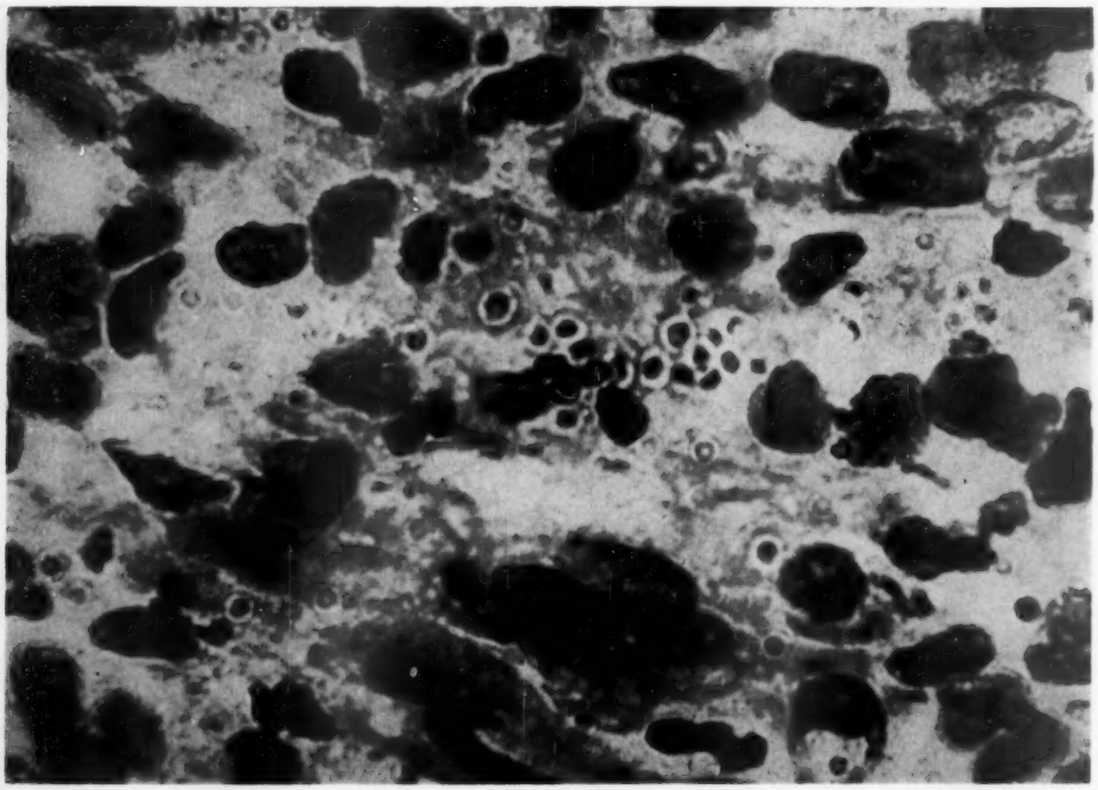

FIG. 4. Photomicrograph of tongue ulcer biopsy specimen showing many histoplasma; hematoxylin and eosin stain.

FIG. 5. Tuberculated chlamydospores of H. capsulatum as they appear on culture (Sabouraud medium) at room temperature (thirty-five-day growth).

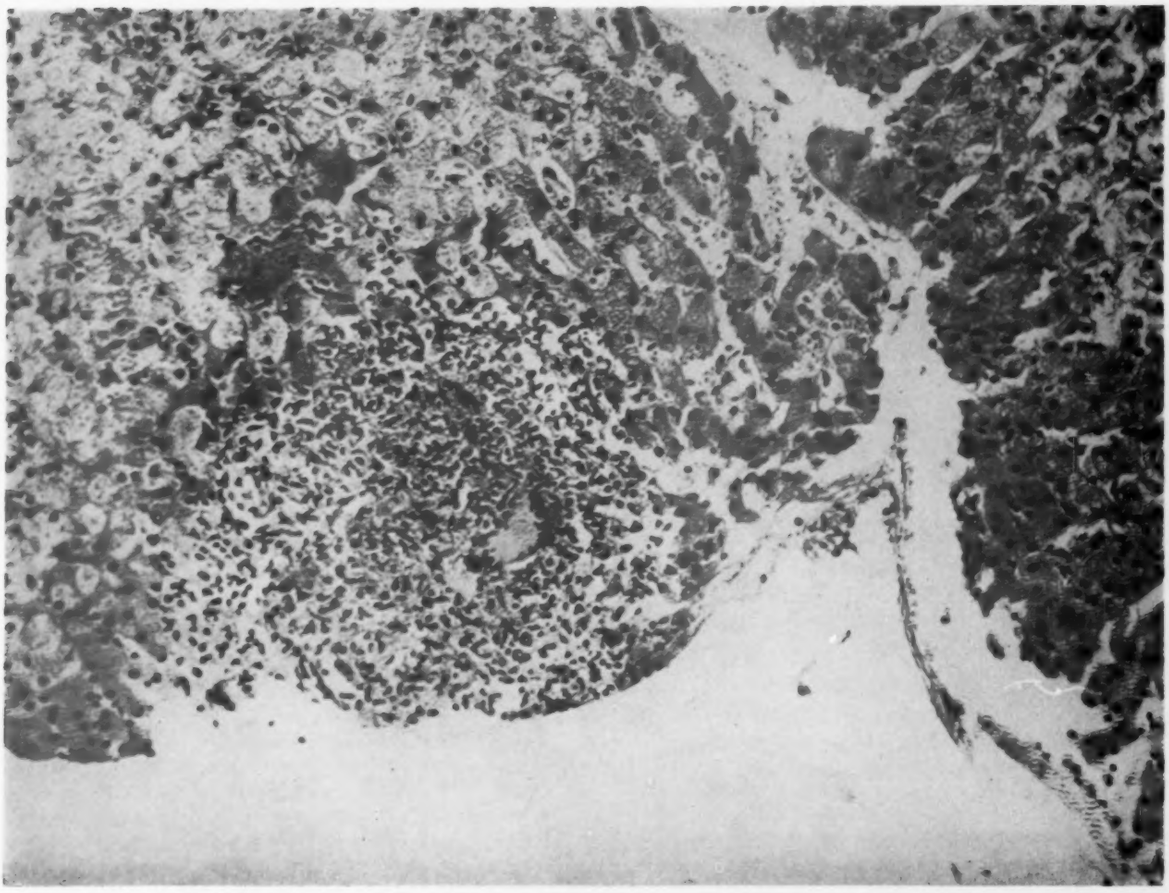

FIG. 6. Photomicrograph of needle biopsy specimen of the liver showing a single small granuloma containing a giant cell.

were discovered. Both lungs showed extensive miliary seeding along with many larger nodules. The liver and spleen were covered with purulent exudate, but on cut surface nothing abnormal could be demonstrated despite careful scrutiny. The adrenals showed no abnormalities.

In the lower one-third of the esophagus multiple ulcerations were found, some having a tendency to confluency. One of these contained a 5 mm., longitudinal perforation. (Fig. 7.) The stomach showed no abnormalities. The small intestine was studded with a vast number of serpiginous-appearing, mucosal ulcers, the long axis of which lay transversely. Most of these ulcers traversed about two-thirds the circumference of the bowel wall and had eroded into the muscularis. At a point 5 cm. proximal to the ileocecal junction one of these ulcers was noted to have perforated through an opening measuring 5 mm. in diameter. Extensive ulceration was also encountered throughout the large intestine. The cecum was practically denuded of mucosa, with only a few interspersed mucosal strands remaining. (Fig. 8.) Ulcerations extended throughout the remainder of the large bowel but became progressively smaller and less numerous until, in the sigmoid and rectum, they were scattered and only about 1 cm. in diameter. No perforation of the large intestine was noted.

Except for the presence of caseous tracheobronchial lymph nodes, no other abnormalities were encountered. The anatomic diagnoses were disseminated histoplasmosis and pulmonary tuberculosis.

Microscopic examination showed the lungs to be involved in a diffuse tuberculous process. Multiple areas of caseation were noted, with a lymphocyte reaction at the periphery and surrounding fibrosis. Langhans' giant cells were seen in profusion. The cavity in the right upper lobe showed a caseous inner layer surrounded by fibrous tissue densely infiltrated with lymphocytes. Patchy areas of edema were present. In spite of a concerted search no histoplasma could be demonstrated either in hematoxylin and eosin or in periodic acid-Schiff (PAS) stains. Ziehl-Neelsen stains demonstrated innumerable acid-fast bacilli.

Multiple discrete granulomas of the liver were encountered comprised of epithelioid cells and typical Langhans' giant cells. Special stains failed to reveal acid-fast bacilli or histoplasma. The spleen also

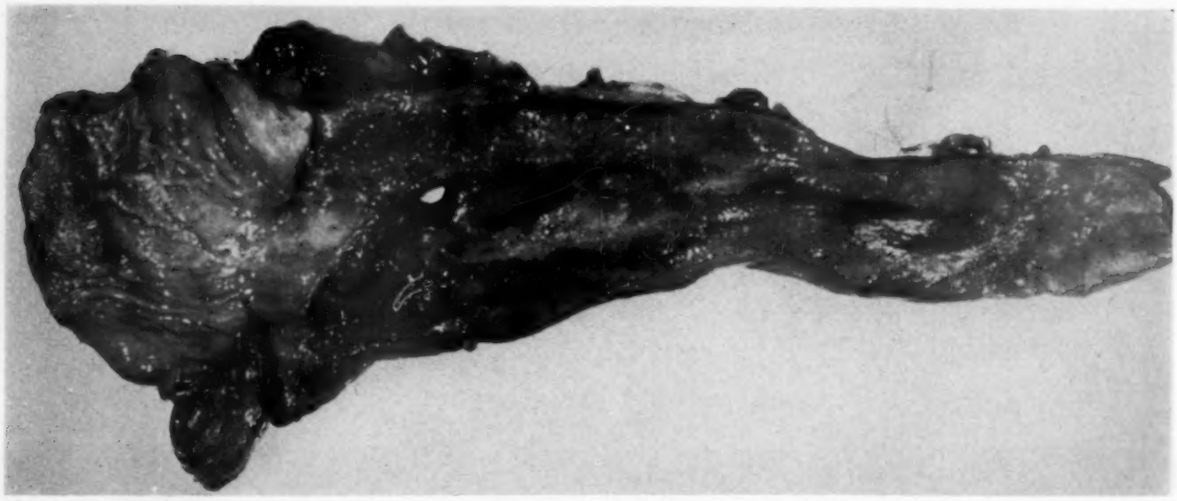

FIG. 7. Photograph of the esophagus showing extensive areas of ulceration and site of perforation.

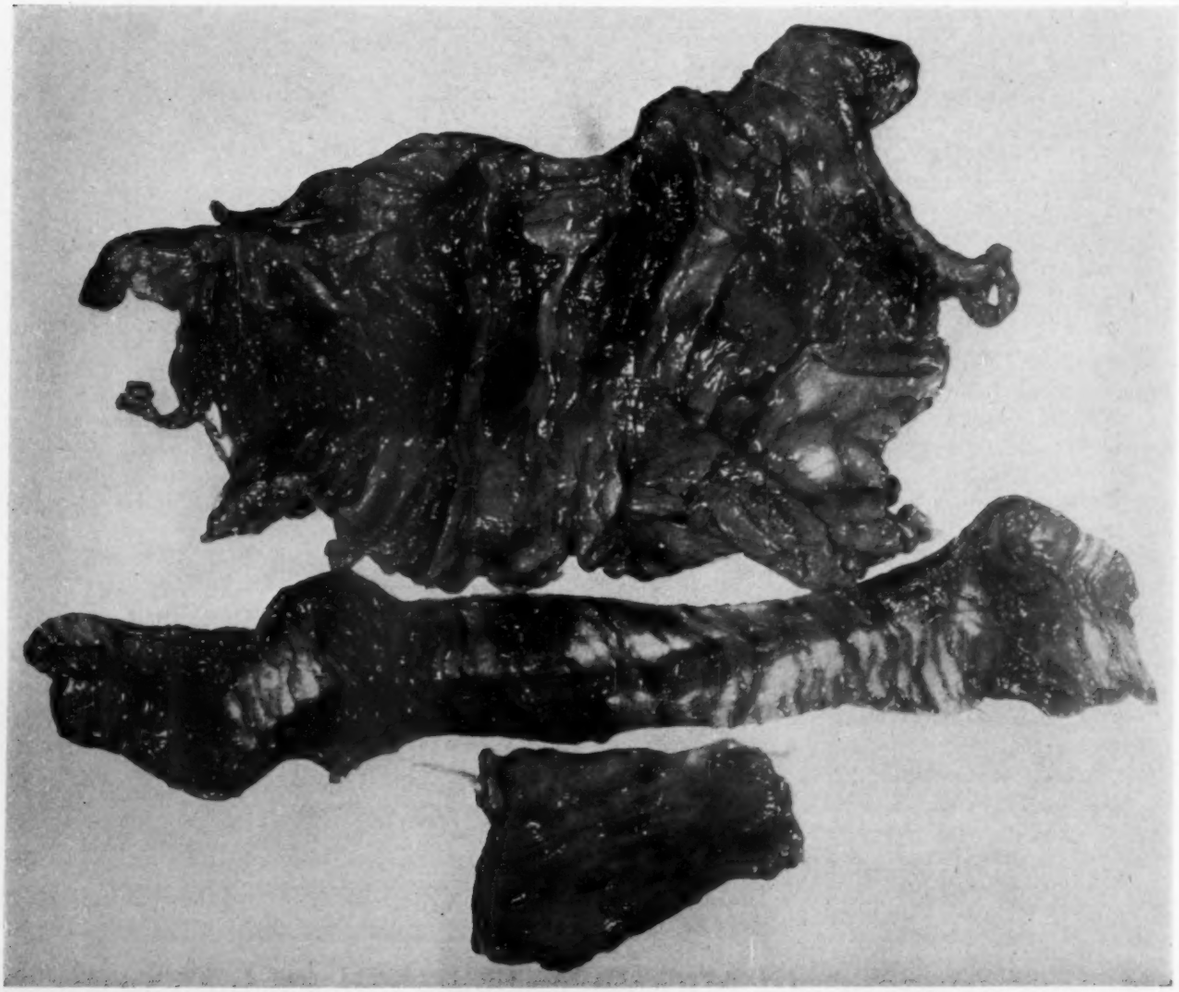

FIG. 8. Photograph of portions of the cecum (above), small intestine and rectum showing areas of ulceration.

presented an occasional granuloma similar to those in the liver. Special stains were negative. The adrenals were normal histologically.

Microscopically all the ulcerations of the gastrointestinal tract were essentially the same. The mucosa was absent in these areas. The depths of the ulcers showed a chronic inflammatory response with many lymphocytes, plasma cells and some polymorphonuclear leukocytes extending into the muscularis. The serosal surface was covered with purulent exudate. After exhaustive study one small clump of round, red bodies, somewhat suggestive of histoplasma, was seen. These were not diagnostic and were not visualized in PAS-stained sections. On the other hand, acid-fast bacilli were present in abundance in all the ulcers studied. Multiple sections through the tongue showed fibrosis and some persistent granulomatous element but there was no evidence of histoplasma in hematoxylin and eosin, or PAS stains. The bone marrow contained a few scattered granulomas but Ziehl-Neelsen and PAS stains gave negative results.

Many cultures from the lungs, liver, tongue and bowel failed to reveal H. capsulatum. Tubercle bacilli were readily isolated from the lungs.

The final diagnoses were (1) chronic pulmonary tuberculosis with dissemination to the liver, spleen, esophagus, small and large bowel, and bone marrow; (2) peritonitis, secondary to perforation of a tuberculous ulceration of the ileum; (3) mediastinitis and left empyema secondary to perforation of a tuberculous ulceration of the esophagus; and (4) histoplasmosis of the tongue, apparently healing. It is conceivable that the granulomas of the liver, spleen and bone marrow, and some of the lesions in the intestine, were due to histoplasmosis but no definite supporting evidence for this contention could be obtained.

COMMENT

In retrospect, it appears that histoplasmosis was of secondary importance in this case for, although it might have eventually proved fatal, the cause of death was severe gastrointestinal tuberculosis with multiple perforations of the alimentary tract leading to mediastinitis, empyema and generalized peritonitis. However, since this is a most unusual complication under antituberculous therapy the possibility still exists that the histoplasmosis could conceivably have contributed in some way to the apparent exacerbation of the tuberculosis. Certainly, it is a rather remarkable coincidence that the tuberculous process should have suddenly become fulminating at the time of appearance of the mycotic lesion. Nevertheless, since this is little more than speculation and without support from the literature, one must assume that histoplasmosis was merely an incidental occurrence.

It is not difficult to understand why the tongue lesion was so misleading. Ulcerative oral lesions are a common manifestation of disseminated histoplasmosis. When solitary, they generally have the appearance of carcinoma. Of the cases reviewed by Weed and Parkhill,[12] 33 per cent of the patients had oral lesions as a part of the presenting complaint. In cases in which adequate follow-up studies were available, these patients almost invariably succumbed to disseminated histoplasmosis. Similarly, in this case, once the diagnosis of histoplasmosis was made, subsequent findings were ascribed to systemic spread. In fact the presence of a small granuloma in a liver biopsy specimen seemed to add considerable support to this contention. When evidence of peritonitis ensued, it seemed fairly obvious that a gastrointestinal tract lesion had perforated. Logically, but as it turned out erroneously, this was attributed to histoplasmosis, for among the protean manifestations of this disease involvement of the gastrointestinal tract is quite prominent.

The prompt spontaneous healing of the oral lesion is another point of exceptional interest. It is tempting to assume that this was a benign, self-limited type of histoplasmosis localized in the mouth but similar in its behavior to the mild transient pulmonary form of the disease which is now known to occur. Any such conclusion is, of course, in direct opposition to the literature wherein recorded cases of alimentary tract lesions have almost invariably been associated with progressive disseminated disease.

The spontaneous regression of the mycotic ulcer in this case, or at least its apparent healing in response to nothing more potent than salt water mouth washes, reflects some doubt on the assumed successes of other therapeutic measures. In 1950 a case similar to ours was reported[4] in which a tongue ulcer due to histoplasmosis appeared in a patient with bilateral fibrocavitary pulmonary tuberculosis. Because the ulcer healed following treatment with sulfanilamide and histoplasmin vaccine, the authors attributed a "cure" to these agents. More recently, Nejedly and Baker[13] reported a case of histoplasmosis apparently localized to the buccal cavity, wherein the lesions healed over a period of several months under intensive therapy with 2-hydroxystilbamidine. The authors therefore concluded that "2-hydroxystilbamidine is an effective agent in the treatment of Histoplasma capsulatum infection" and recommended that further evaluation of the efficacy of this drug be carried out.

While no certain conclusions can be drawn from these comparisons, and we are personally inclined to doubt the benefit of any known form of chemotherapy in histoplasmosis, it would at least seem advisable to be extremely cautious in evaluating the effectiveness of various therapeutic measures in a disease which is often benign and which may undergo spontaneous regression.

Perhaps the most intriguing aspect of this case is that the first evidence of histoplasmosis became manifest only after twenty-one consecutive months of hospitalization for active pulmonary tuberculosis. The tendency for a prolonged latent period between infection and rapid progression is well known. In a number of disseminated cases a history of chronic oral ulcers of several years' duration has been elicited.[12] However, in this case the ulcer on the patient's tongue was definitely of recent onset, and there is some further reason to believe that the disease may have been contracted in the hospital. During the last year of hospitalization the patient had spent much of his time at basket weaving and carpentry of a minor sort. Because he frequently held the reeds in his mouth while weaving, the idea occurred that this might have had some bearing on the etiology of his disease; therefore a supply of reeds was obtained which were then cut into small segments and rinsed in sterile saline for several days. The sediment which collected in the saline was injected intraperitoneally into mice suitably protected from pyogens by administration of penicillin and streptomycin. Of thirty mice so injected eight died within the first week; the remainder were sacrificed at intervals of three to six weeks. Almost all had local abscess formation at the site of injection. Six had evidence of systemic abscesses of the liver and spleen. In none could H. capsulatum be identified by culture or specially stained tissue sections. Even though these studies proved negative, they are cited as a matter of interest. Wood has been involved as a vehicle of infection in a number of epidemics of histoplasmosis,[14] and H. capsulatum has now been cultured from sawdust and soil.[15] Therefore it still seems possible that the reeds which the patient handled bore the chlamydospores of this organism, particularly since they are imported from Mexico, a known endemic area.

SUMMARY AND CONCLUSIONS

1. A case of coexisting tuberculosis and histoplasmosis of the alimentary tract is presented. Tuberculous involvement of the esophagus, small intestine and colon was unusually extensive and severe, with death resulting from esophageal and ileal perforations. A single ulceration attributable to histoplasmosis was apparently confined to the oral cavity and benign in its behavior. The lesion underwent spontaneous regression and does not appear to have contributed to the events leading to the patient's demise. Certain interesting implications of this case are discussed.

2. The theory that the patient contracted oral histoplasmosis while in the hospital from reeds used in basket making is intriguing but unproved.

REFERENCES

1. Hodgson, C. H., Weed, L. A. and Clagett, O. T. Pulmonary histoplasmosis: summary of data on reported cases and a report on two patients treated by lobectomy. *J. A. M. A.*, 145: 807, 1951.
2. Bunnell, I. L. and Furcolow, M. L. A report of ten proved cases of histoplasmosis. *Pub. Health Rep.*, 63: 299–316, 1948.
3. Hausman, R. and Hiemstra, S. Een geval van tuberculose en histoplasmose. *Med. maandbl.*, 2: 369, 1949.
4. Brachetto-Brian, D. and Ugazio, D. A. Histoplasmosis medio lingual. *An. Inst. Med. Exper. (Buenos Aires)*, 2: 213, 1950.
5. Clinico-pathologic conference. Miliary pulmonary infiltration with hydrothorax and ascites. *Am. J. Med.*, 11: 757–764, 1951.
6. Orr, T. G. and Wilson, S. J. Some surgical aspects of histoplasmosis. *Am. Surgeon*, 18: 109, 1952.
7. Sutliff, W. D., Hughes, F., Ulrich, E. and Burkett, L. L. Active chronic pulmonary histoplasmosis. *Arch. Int. Med.*, 9: 571, 1953.
8. Salvin, S. B. and Furcolow, M. L. Precipitins in human histoplasmosis. *J. Lab. & Clin. Med.*, 43: 259, 1954.
9. Vivian, D. N., Weed, L. A., McDonald, J. R., Clagett, O. T. and Hodgson, C. H. Histoplasmosis: clinical and pathological study of 20 cases. *Surg., Obst. & Gynec.*, 99: 53, 1954.
10. Peabody, J. W., Jr. and Murphy, J. D. Dual granulomatous disease due to the deep mycoses coexisting with active pulmonary tuberculosis Read before the annual meeting of the Southern Trudeau Society, Atlanta, Ga., Sept. 10, 1954. To be published.
11. Transactions of the 14th Va-Army-Navy Conference on The Chemotherapy of Tuberculosis. To be published.
12. Weed, L. A. and Parkhill, E. M. The diagnosis of histoplasmosis in ulcerative disease of mouth and pharynx. *Am. J. Clin. Path.*, 18: 130, 1948.
13. Nejedly, R. F. and Baker, L. A. Treatment of localized histoplasmosis with 2-hydroxystilbamidine. *Arch. Int. Med.*, 95: 37–40, 1955.
14. Grayston, J. T. and Furcolow, M. L. The occurrence of histoplasmosis in epidemics: epidemiological studies. *Am. J. Pub. Health*, 43: 665–676, 1953.
15. Loosli, C. G., Grayston, J. T., Alexander, E. R. and Tanzi, F. Epidemiological studies of pulmonary histoplasmosis in a farm family. *Am. J. Hyg.*, 55: 392–401, 1952.

Isolated Bilateral Simultaneous Dissection of the Renal Arteries*

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THE following report of a case of dissecting "aneurysm" is believed to be unique in the medical literature.

The patient (Hospital No. 222–704) was first admitted to The University Hospitals of Cleveland in 1942 for treatment of a corneal ulcer. His admission blood pressure was 144/108 mm. Hg; subsequent readings showed a systolic range of 108 to 132 and diastolic of 80 to 102. Urinalysis revealed: acid; specific gravity 1.030; albumin +; sugar 0; 3 to 4 white blood cells per high power field. He was treated by fever therapy (two chills from killed typhoid bacilli) and discharged improved after three days. He was not seen again until his second and final admission to University Hospitals in 1954. During the afternoon of April 11, 1954, steady, non-radiating bilateral costovertebral angle pain with concurrent epigastric pain developed. The pain became so severe that the patient came to the Emergency Ward at 2 A.M. the following morning. Physical examination was negative except for a fever of 38.2°C. The urinary sediment was filled with red blood cells, however, and the patient was admitted to the hospital later that day (April 12th). Past history and systemic review at the time of admission were non-contributory except for the following: on two occasions during the previous year the patient had excreted a few drops of bright red blood on emptying the urethra following urination. There were no other symptoms and the patient did not consult a physician. Physical examination revealed the following: temperature, 36°C.; pulse, 76; respirations, 18; and blood pressure, 140/100. The patient was a well developed, well nourished, lethargic fifty-seven year old white man. There was mild bilateral costovertebral angle tenderness. One ecchymotic area was noted on the left arm. There were no other pertinent physical findings. X-ray films did not show a ureteral calculus. An intravenous pyelogram revealed no excretion of the contrast material up to eighty minutes after injection. Retrograde pyelograms were negative except for slight blunting of several of the minor calyces. On one of the retrograde films made after removal of the catheter there was evidence of backflow. Laboratory findings are summarized in Table 1. The patient's blood pressure remained at a constant level from the time of admission to the morning of the second hospital day. That noon, however, his blood pressure rose to 222/120. Twenty-five minutes later he had a generalized tonic convulsion. Anticonvulsant therapy was begun. The patient had a second convulsion at 2:30 P.M. but none thereafter, and anticonvulsant therapy was discontinued after about twenty-two hours. His blood pressure readings following the rise which immediately preceded the convulsions are seen in Table 1. His urine, which had been grossly "hazy" or "cloudy," became grossly bloody by the second hospital day, assumed the appearance of pure blood by the third hospital day, and continued to appear so throughout the remainder of his hospital course. By the fourth hospital day the patient had several scattered ecchymoses. The clotting time in both glass and silicone-coated tubes was prolonged. This was associated with a normal prothrombin time but a greatly prolonged clotting time of a mixture of bovine thrombin and the patient's oxalated plasma. This defect alone, however, was probably not enough to account for the prolonged clotting time. No therapy was given. The patient's condition slowly became worse; during the fifth hospital day he was occasionally disoriented and by the sixth day death seemed imminent.

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TABLE 1

Findings	Hospital Day							
	Admission	1	2	3	4	5	6	7
Urine:								
Method of collection	Voided	Voided	Voided	Voided	.....	Catheterized	Catheterized	.....
Specific gravity	.....	1.010	.....	1.015	.....	.....	1.028	.....
Albumin	.....	++	.....	+	.....	.....	++++	.....
Red blood cells per high power field	Abundant	Abundant	.....	Abundant	.....	.....	Abundant	.....
White blood cells per high power field	.....	Occasional	.....	Occasional	.....	.....	Few	.....
Casts	.....	Fine and coarsely granular	.....	.....	.....	.....	.....	.....
Benzidine	.....	++++	.....	++++	.....	.....	++++	.....
Volume, cc.	300	?	110	78	0	50	30	.....
Blood chemistry:								
Urea nitrogen, mg. %	.....	81	108	126	.....	216	242 92	124
Creatinine, mg. %	.....	.....	13.6	.....	.....	23	25	12
CO_2 combining power, mEq./L.	.....	.....	23	.....	15	.....	7 18	.....
Calcium, mg. %	.....	8.4	.....	.....	.....	.....	....	.....
Serum sodium, mEq./L.	.....	.....	140	.....	140	.....	140 136	.....
Serum potassium, mEq./L.	.....	.....	4.5	.....	.....	5.0	6.4 6.4	6.7
Blood pressure:								
Systolic	140	150–162	222 148–190	164–200	130–150	110–150	68–140	124–132
Diastolic	100	80	120 82–110	60–154	42–82	60–75	42–80	68–76

Dialysis by artificial kidney

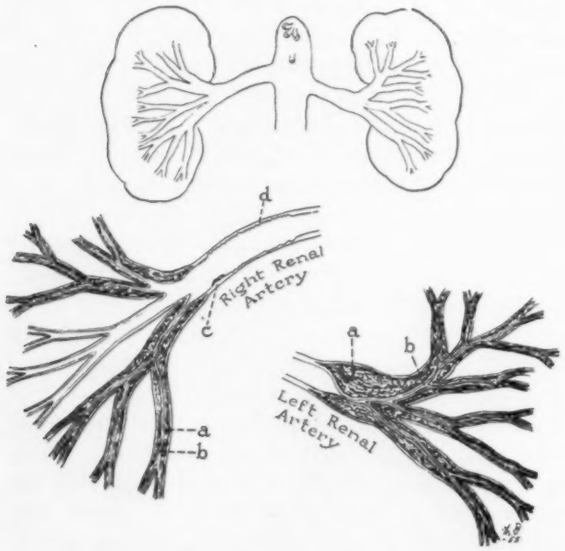

FIG. 1. Diagrammatic representation of the gross description of the renal arteries. See text. a, Dissecting hemorrhage within the media. b, Lumen occluded by intramural hemorrhage. c, Large intimal atheromatous plaque. d, Atheromatous ulcer extending around the entire circumference of the main right renal artery.

That afternoon he underwent dialysis with an artificial kidney of the Skeggs-Leonard type.[1] The dialysis resulted in appreciable decrease in blood urea nitrogen and blood creatinine (Table 1), but the patient did not improve clinically. He died at 1:30 P.M. on the seventh hospital day.

The postmortem examination was limited to the abdomen. Aorta: The abdominal aorta had slightly decreased elasticity. There were numerous intimal atheromatous plaques measuring up to 1.5 cm. in diameter and 0.2 cm. in thickness. Some contained calcium. No dissection was noted in the wall of the aorta. Renal arteries: The abnormalities to be described are shown diagrammatically in Figure 1. The orifices of both renal arteries were patent. Beginning at a point 1 cm. from its origin, the left renal artery and its intrarenal branches appeared to be occluded by a dark red thrombus. (Fig. 2.) On section, what was at first thought to be a thrombus proved to be an intramural hematoma which had collapsed the lumen. (Figs. 1A, 1B and 3.) The lumen of the right renal artery was patent until division into its major branches occurred. There was an intimal ulcer (Fig. 1D) extending around the entire circumference of the main artery beginning 1 cm. from the origin of the vessel and extending to 0.5 cm. proximal to the division of the artery into its branches. Two of the three branches of the right renal artery had the same type of intramural dissection and hematoma formation with resultant occlusion of the lumen as described for the left main renal artery. There was no continuity between the intimal ulcer and these dissections. Genitourinary system: The right kidney weighed 220 gm. and the left 190 gm. The kidneys had a

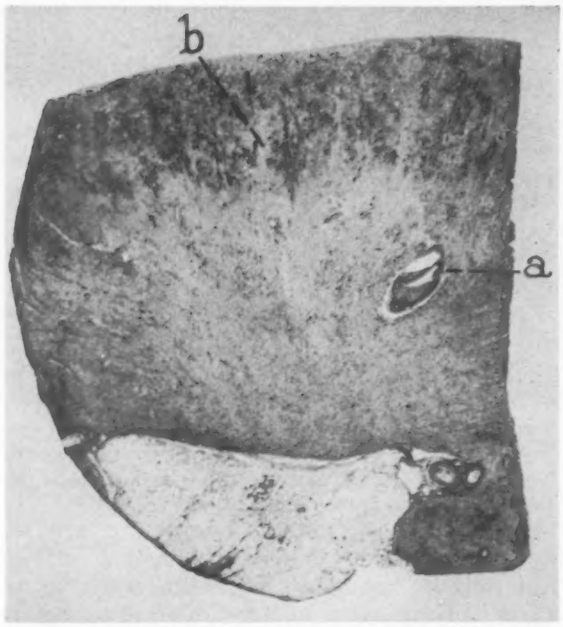

FIG. 2. Section through the left kidney (original magnification × 4.8). Elastic tissue van Gieson stain; a, involved artery deep in the kidney. This is the same artery as seen in Figures 3 and 5; b, cortex of kidney.

FIG. 3. The same artery as in Figures 2 and 5 (original magnification × 35; hematoxylin and eosin stain). a, Intramural dissecting hemorrhage within the media. b, Outer portion of media. c, Inner portion of media.

similar appearance. The capsules stripped with ease exposing a smooth, glistening external surface which was mottled dark red and yellow. The dark red areas averaged 0.1 cm. in diameter and in some areas their margins were confluent. The cut surface was flat. The cortical striations were accentuated, being made up of alternating radial dark red and yellow lines averaging 1 mm. in width. The margin between cortex and medulla was blurred but the medullary markings were not unusual and no blunting of the pyramids was seen. The cut surface of the left kidney showed a yellow triangular area with its base at the outer edge, measuring 0.5 cm. across the base and 0.7 cm. in height. This area was sharply demarcated by a dark red line; its surface was moderately soft and granular. Both kidney pelves contained dark red clotted blood; there was no dilatation. The renal veins were patent throughout. The bladder had recent submucosal hemorrhage in the region of the trigone but was otherwise normal.

Microscopically, there was dissection by recent hemorrhage between the outermost layers of the media of the left renal artery and of branches of the right renal artery, with formation of an intramural clot, causing the intimal surfaces to collapse into apposition. In some vessels this dissection involved all but a small arc of the circumference of the media. The findings extended throughout the interlobar arteries and included some arteries deep within the kidney substance. (Figs. 2 and 3.) Within the cortex of both kidneys there were scattered, poorly defined, frequently coalescent areas of hemorrhage into the edematous interstitial tissue. Within these areas there was tubular degeneration and necrosis associated with the interstitial and intraluminal hemorrhage. The extent of involvement of the two kidneys was similar. Also seen in the cortex were focal scars with varying degrees of parenchymatous atrophy. In many of these scars there were one or several hyalinized glomeruli and focal areas showing mononuclear exudation. Some of the glomeruli showed capsular adhesions and focal hyalinization of the tufts. Most of these changes were focal, however, and the majority of the glomeruli were well preserved. There was blood in both the proximal and distal convoluted tubules but hemorrhage was seen infrequently in glomeruli, and then only in those that were the seat of marked hyalinzation. Protein and pigment casts were seen in the distal convoluted tubules. In one area of the left kidney there was a recent hemorrhagic infarct and the vessel related to this infarct showed a hyaline necrotic change in the media.

The final pathologic diagnoses were: (1) dissecting "aneurysms" of left renal artery and branches of right renal artery; (2) early bilateral cortical necrosis of kidneys with interstitial and intratubular hemorrhage; (3) medial de-

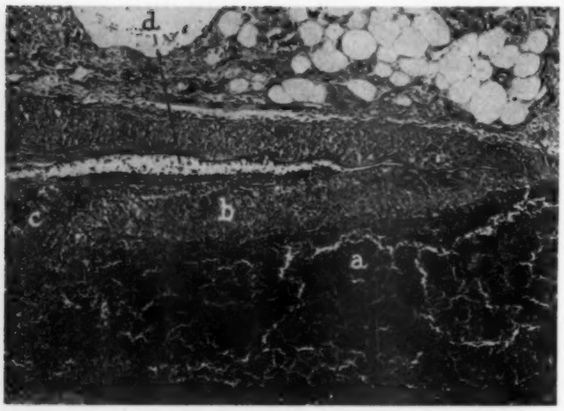

FIG. 4. Section through a renal artery of the right kidney (original magnification × 100; hematoxylin and eosin stain). a, Intramural hemorrhage. b, Normal media. c, Degenerated media. d, Compressed arterial lumen.

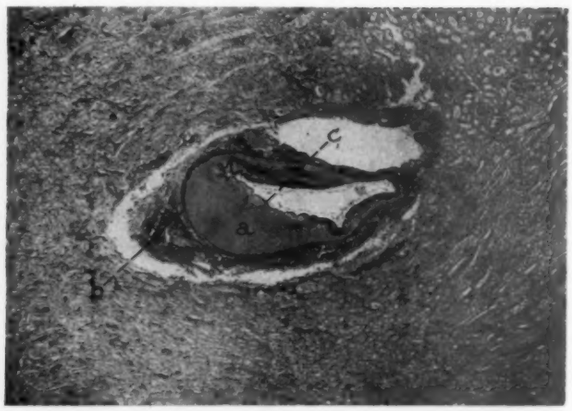

FIG. 5. The same section and magnification (× 35) as in Figure 3; elastic tissue van Gieson stain. a, Intramural hemorrhage. b, Intact external elastic membrane. c, Intact internal elastic membrane.

generation and necrosis of renal arteries; (4) hemorrhagic infarct of left kidney; and (5) focal glomerulonephritis, slight.

COMMENTS

Isolated dissecting aneurysm unrelated to trauma has been reported in the left internal carotid artery,[2] a coronary artery[3] and a cerebral artery.[4] Shennan[5] gives references to others but some of these were traumatic in origin. There are many reports of true aneurysms of the renal artery and of false aneurysms following trauma. We have been unable to find any reference to isolated intramural dissection of the renal artery, that is, dissection arising within the renal artery itself and not occurring as an extension of dissection of the aorta or as a result of trauma.* The case reported herein is remarkable because it demonstrated this unique abnormality. It is additionally noteworthy because the primary renal artery dissection occurred bilaterally and because the bilateral occurrence was simultaneous.

The precipitating cause of dissection of these renal arteries is difficult to assess. Microscopically, there was medial degeneration. The degeneration involved smooth muscle (Fig. 4); the elastic tissue was uninvolved. (Fig. 5.) This is the combination of findings reported by Gore and Seiwert[11] and Gore[12,13] in dissecting "aneurysm" of the aorta in the older age group, in which hemorrhage apparently originates within the media from weakened vasa vasorum. Evidence of a reparative reaction to the medial degeneration, as described by them, is missing, however. In view of the marked atherosclerosis of the renal arteries, as evidenced particularly by the large atheromatous ulcer in the right renal artery, one must consider the possibility of atheromatous involvement of the media with dissection through the base of the ulcer into a weakened media. This cannot be definitely ruled out, of course, but seems unlikely on a statistical basis. Shennan[5] found such a cause of dissecting aneurysm in only six of 218 cases of recent dissecting aneurysms of the aorta. Furthermore, it would require a high order of coincidence for such an unusual onset to occur in at least three places (left renal artery and the two main branches of the right renal artery) simultaneously.

The question arises as to what changes in blood pressure might be expected in an individual in whom both kidneys are practically completely infarcted. In the case reported herein, the patient's blood pressure was relatively normal during the two-day period from the time of admission to noon of the second hospital day, particularly in relation to his known blood pressure at the time of his first hospital admission twelve years previously (144/108). It is reasonable to assume that during this two-day period renal blood flow was markedly reduced since it is known that the larger renal arteries were in

* The three cases[6–9] referred to by Abeshouse[10] are reports of true or false renal artery aneurysms and make no mention of the type of intramural dissection which is the subject of this paper. Penkert's case[7] is one of traumatic intramural hematoma of a small branch of a renal artery.

process of occlusion or were already occluded. Under these circumstances renin may have been escaping through the renal veins.[14] However, there was no unusual hypertension until the sudden rise noted at noon of the second hospital day. This ultimate blood pressure elevation suggests, perhaps, that the excretion of pressor substances finally exceeded a critical level and resulted in a prompt rise of blood pressure. The disappearance of the hypertension after the third hospital day might be conversely explained. It was not the result of the anticonvulsant therapy because this had been discontinued after about twenty-two hours. It is possible that further diminution in blood flow through the kidneys resulted in such reduced venous outflow that not enough pressor substance was excreted to maintain the hypertension.

The azotemia present in this patient was rapidly progressive and produced severe clinical symptoms which did not respond to dialysis with the artificial kidney. The histologic changes observed in the kidneys indicated that there probably had been severe impairment of renal blood flow for several days before death. Since the patient was asymptomatic until the day before admission it may be assumed that the acute episode was limited to the duration of observation. The urine output during the time of observation was far too small to contribute significantly to the excretion of nitrogen. There was no diarrhea or extraneous fluid loss and no protein intake by mouth. The blood urea nitrogen was determined on six of the last seven days of observation and the average increase over five twenty-four-hour periods was 32 mg. per 100 ml. per twenty-four hours. In a patient weighing 70.3 kg. (the patient's weight on admission), with an assumed total body water of 65 per cent of body weight, no protein intake and equal distribution of the urea formed, this increase would represent the formation of 14.6 gm. of urea nitrogen every twenty-four hours. This would require the breakdown of 91.3 gm. of protein per twenty-four hours for urea production alone. The blood urea nitrogen may vary from approximately 30 per cent of the total non-protein nitrogen in the normal to as high as 80 per cent in severe renal failure.[15] The use of either of these extreme figures to calculate the total nitrogen production would indicate the breakdown of large quantities of body proteins per twenty-four hours. This is in no sense to be construed as a balance study, but with essentially no excretion of nitrogen and no intake, these values must represent an approximation of the endogenous breakdown. Thus, this rate of increase of the urea nitrogen is very rapid and consistent with complete cessation of renal function associated with an increase in protein catabolism above that seen with simple starvation[16] or surgical stress[17] aside from bone fractures. These former states may cause the loss of 10 gm. of total nitrogen per day, on the average, or the breakdown of approximately 63 gm. of body protein. The increase in potassium in this case is rather minimal compared to that seen in post-traumatic renal insufficiency[18] in which large areas of necrotic or infected tissue may be present and the usual ratio of potassium to nitrogen loss is increased above that seen with moderate stress.[17,18] Therefore, it would seem that in this situation we are dealing with a marked protein catabolic response brought about by unknown stimuli and not associated with tissue trauma or infection, aside from the ischemic kidneys which were largely excluded from the general circulation.

The artificial kidney was used to treat the clinical uremic state in this patient because acute, reversible renal disease was suspected. Onset of symptoms (chiefly pain) had been sudden, there was no past history of chronic inflammatory renal disease and retrograde pyelograms had demonstrated normal or large kidneys. Even severe clinical uremia, if acute in origin, will usually respond well to dialysis. In this instance the major indication for dialysis was the patient's steadily deepening stupor; the potassium was not dangerously elevated. The chemical results of dialysis were good but the clinical response was poor. No lessening of stupor was noted by the observers. This failure is unexplained but speculation concerning a relationship between the excessive protein catabolism, severe clinical uremia and lack of response to dialysis is of interest in terms of relative rates of formation and removal of specific, potentially toxic substances and/or severe brain cell damage.[19]

SUMMARY

1. A case of intramural renal artery dissection is reported. The lesion was simultaneously bilateral, was not preceded by trauma and was not associated with intramural dissection of the aorta. It is believed to be the first

case of isolated, non-traumatic intramural dissection of the renal artery to be reported.

2. The nature of the arterial disease, the blood pressure changes and the marked elevation of blood nitrogen are discussed.

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REFERENCES

1. Skeggs, L. T., Jr., Leonards, J. R. and Heisler, C. R. Artificial kidney. II. Construction and operation of an improved continuous dialyzer. *Proc. Soc. Exp. Biol. & Med.*, 72: 539, 1949.
2. Jentzer, A. Dissecting aneurysm of the left internal carotid artery. *Angiology*, 5: 232, 1954.
3. Schmid, H. J. Dissecting aneurysm of a coronary artery. *Schweiz. med. Wchnschr.*, 81: 1170, 1951.
4. Sinclair, W. Dissecting aneurysm of the middle cerebral artery associated with migraine syndrome. *Am. J. Path.*, 29: 1083, 1953.
5. Shennan, T. Dissecting aneurysms. Medical Research Council, Special Reports. No. 193. London, 1934. His Majesty's Stationery Office.
6. Morris, H. Aneurysm of the renal artery. *Lancet*, 2: 1002, 1900.
7. Penkert, M. Internal hemorrhage as the result of rupture of a dissecting aneurysm of the kidney following trauma. *Aerztl. Sachverst.-Ztg.*, 7: 221, 1901.
8. Reeves, H. A. The treatment of ruptured kidney. *Lancet*, 2: 588, 1884.
9. Turner, F. C. Transactions of the Pathological Society of London, p. 277, 1885.
10. Abeshouse, B. S. Aneurysm of the renal artery: report of two cases and review of the literature. *Urol. & Cutan. Rev.*, 55: 451, 1951.
11. Gore, I. and Seiwert, V. J. Dissecting aneurysm of the aorta. *Arch. Path.*, 53: 121, 1952.
12. Gore, I. Pathogenesis of dissecting aneurysm of the aorta. *Arch. Path.*, 53: 142, 1952.
13. Gore, I. Dissecting aneurysms of the aorta in persons under forty years of age. *Arch. Path.*, 55: 1, 1953.
14. Goldblatt, H. The renal origin of hypertension. *Physiol. Rev.*, 27: 120, 1947.
15. Peters, J. P. and Van Slyke, D. D. Quantitative Clinical Chemistry, 2nd edition. Baltimore, 1946. Williams and Wilkins Co.
16. Benedict, F. G. A study of prolonged fasting. Carnegie Institute of Washington. Pub. 203, 1915.
17. Moore, F. D., Steenburg, R. W., Ball, M. R., Wilson, G. M. and Myrden, J. A. Studies in surgical endocrinology. *Ann. Surg.*, 141: 145, 1955.
18. Teschan, P. E., Post, R. S., Smith, L. H., Abernathy, R. S., Davis, J. H., Gray, D. M., Howard, J. M., Johnson, K. E., Klopp, E., Mundy, R. L., O'Meara, M. P. and Rush, B. F., Jr. Post-traumatic renal insufficiency in military casualties. I. Clinical characteristics. *Am. J. Med.*, 18: 172, 1955.
19. Knutson, J. and Baker, A. B. The central nervous system in uremia. A clinicopathologic study. *Arch. Neurol. & Psychiat.*, 54: 130, 1945.

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3. The Rotation (swivel chair) Test. *The patient sits in a swivel chair with his eyes closed and his head on a level plane. The chair is turned through ten complete revolutions in twenty seconds. Stimulation of a normal labyrinth will cause nystagmus, past pointing of the arms and subjective vertigo.*

Notes on the Diagnosis and Management of "Dizziness"

I. Vertigo

The term "dizziness" (vertigo) should be restricted to the sensation of whirling or a sense of motion.[1] This sensation is usually of organic origin and is the tangible symptom of a specific pathology.

Moderate vertigo, with a sense of motion and a whirling sensation, may be produced by infection, trauma or allergy of the external or middle ear. Examination of the ear will usually disclose the abnormality.

Severe vertigo, which will not permit the patient to stand and causes nausea and vomiting, indicates an irritation or destruction of the labyrinth. The specific condition may be labyrinthine hydrops, an acute toxic infection, hemorrhage or venospasm of the labyrinth or a fracture of the labyrinth. Multiple sclerosis and pathology of the brain stem should be considered also.

It is important to learn if the patient's sensation is continuous or paroxysmal.[2] Paroxysmal vertigo suggests specific conditions: Ménière's syndrome, cardiac disease and epilepsy. Continuous vertigo without a pattern may be due to severe anemia, posterior fossa tumor or eye muscle imbalance.

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---

1. Swartout, R., III, and Gunther, K.: "Dizziness:" Vertigo and Syncope, GP *8*:35 (Nov.) 1953.

2. DeWeese, D. D.: Symposium: Medical Management of Dizziness: The Importance of Accurate Diagnosis, Tr. Am. Acad. Ophth. *58*:694 (Sept.-Oct.) 1954.

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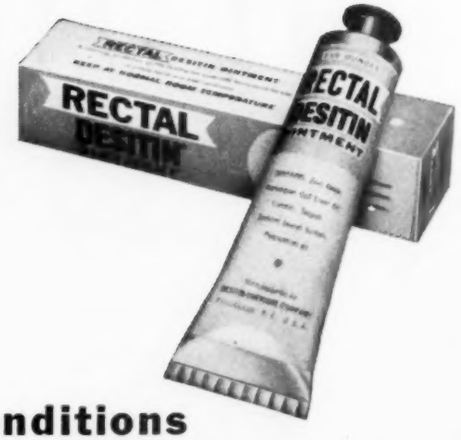

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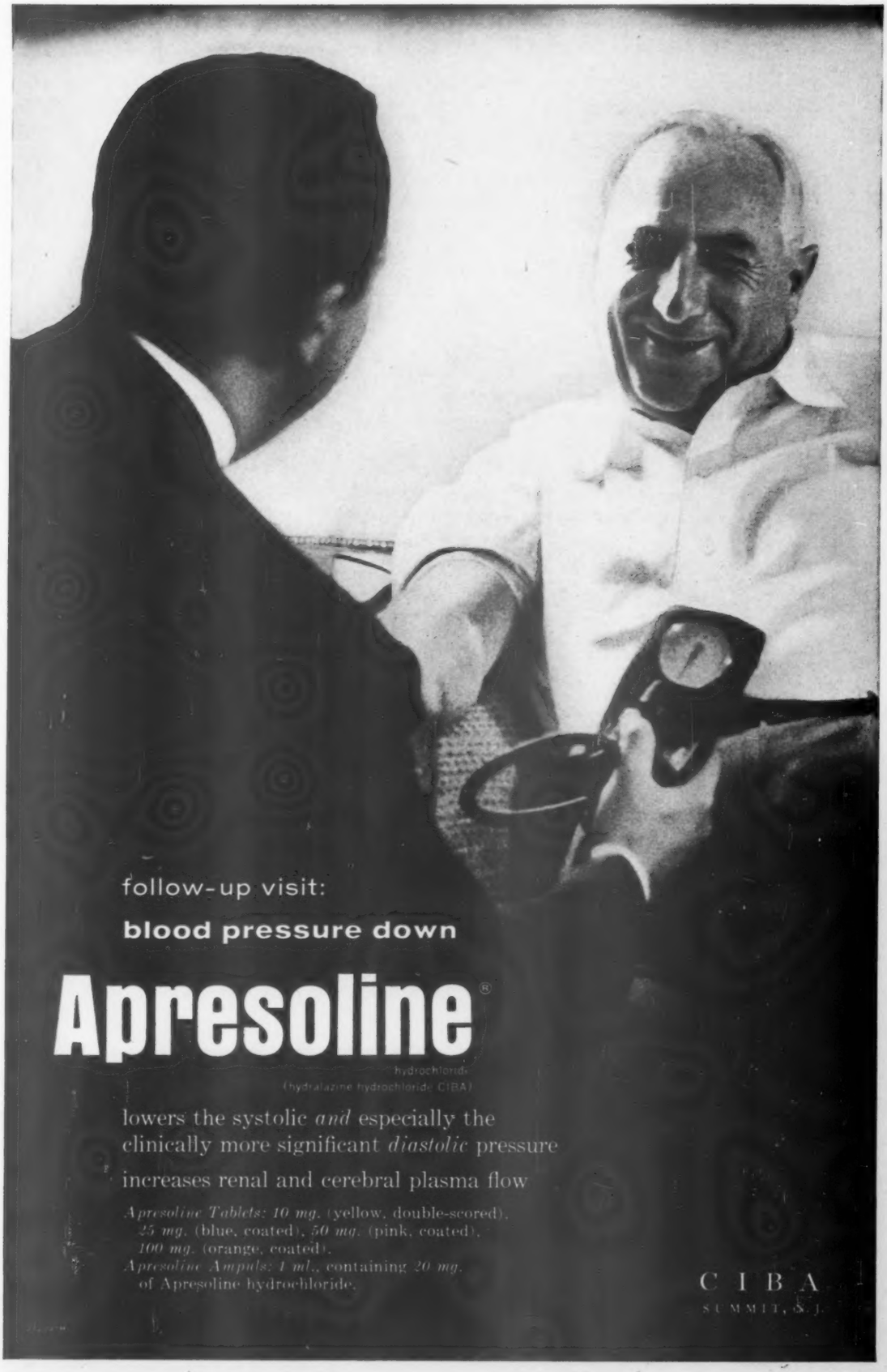
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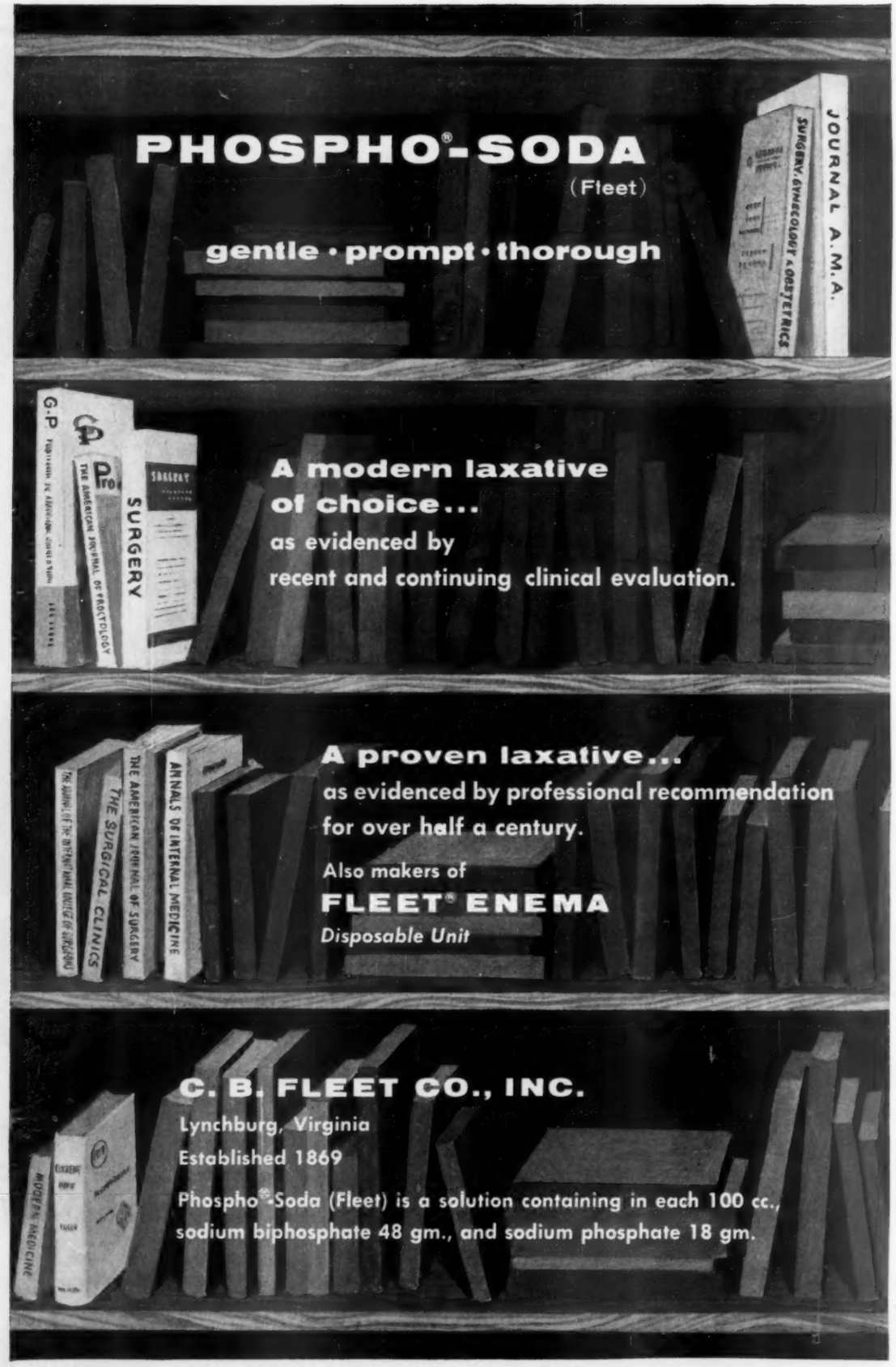
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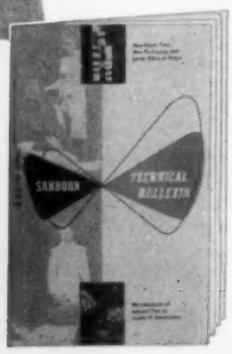

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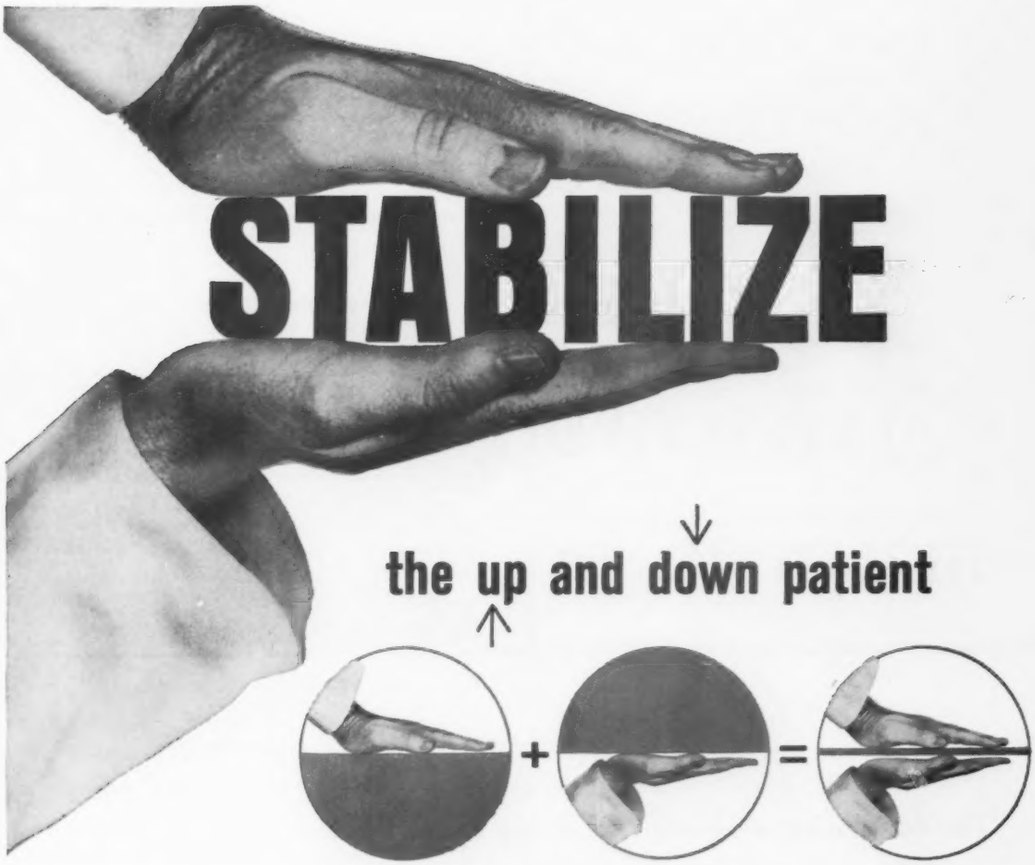

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1. Arnoff, B.: Personal communication. 2. Lazarte, J. A., and Petersen, M.C.: Personal communication.

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Holly, R.G.: Anemia in Pregnancy, Obst. & Gynec. **5**:562 (April) 1955.

Hill, J.M., et al.: Cobalt Therapy in Anemia, Texas J. Med. **51**:686 (Oct.) 1955.

Rohn, R.J.; Bond, W.H., and Klotz, L.J.: The Effect of Cobalt-Iron Therapy in Iron-Deficiency Anemia in Infants, J. Indiana M.A. **46**: 1253 (1953).

Holly, R.G.: Anemia in Pregnancy, Paper delivered before Amer. Congress of Obstetrics and Gynecology (Dec.) 1954.

* Holly, R.G.: The Value of Iron Therapy in Pregnancy, Journal Lancet **74**:211 (June) 1954.

Quilligan, J.J., Jr.: Effect of a Cobalt-Iron Mixture on the Anemia of Prematurity, Texas J. Med. **50**: 294 (May) 1954.

Hamilton, H.G.: The Use of Cobalt and Iron in the Prevention of Anemia of Pregnancy. Paper delivered before the South. Med. Assn.

Rohn, R.J., and Bond, W.H.: Observations on Some Hematological Effects of Cobalt-Iron Mixtures, Journal Lancet **73**:317 (Aug.) 1953.

Holly, R.G.: Studies on Iron and Cobalt Metabolism, J.A.M.A. **158**: 1349 (Aug.13) 1955.

Jaimet, C.H., and Thode, H.G.: Thyroid Function Studies on Children Receiving Cobalt Therapy, J.A.M.A. **158**:1353 (Aug. 13) 1955.

Klinck, G.H.: Thyroid Hyperplasia in Young Children, J.A.M.A. **158**:1347 (Aug. 13) 1955.

Tevetoglu, F.: The Treatment of Common Anemias in Infancy and Childhood with a Cobalt-Iron Mixture. Driscoll Foundation Children's Hosp., Corpus Christi, Texas (April) 1956.

Ausman, D.C.: Cobalt-Iron Therapy in the Treatment of Some Common Anemias Seen in General Practice, in press.

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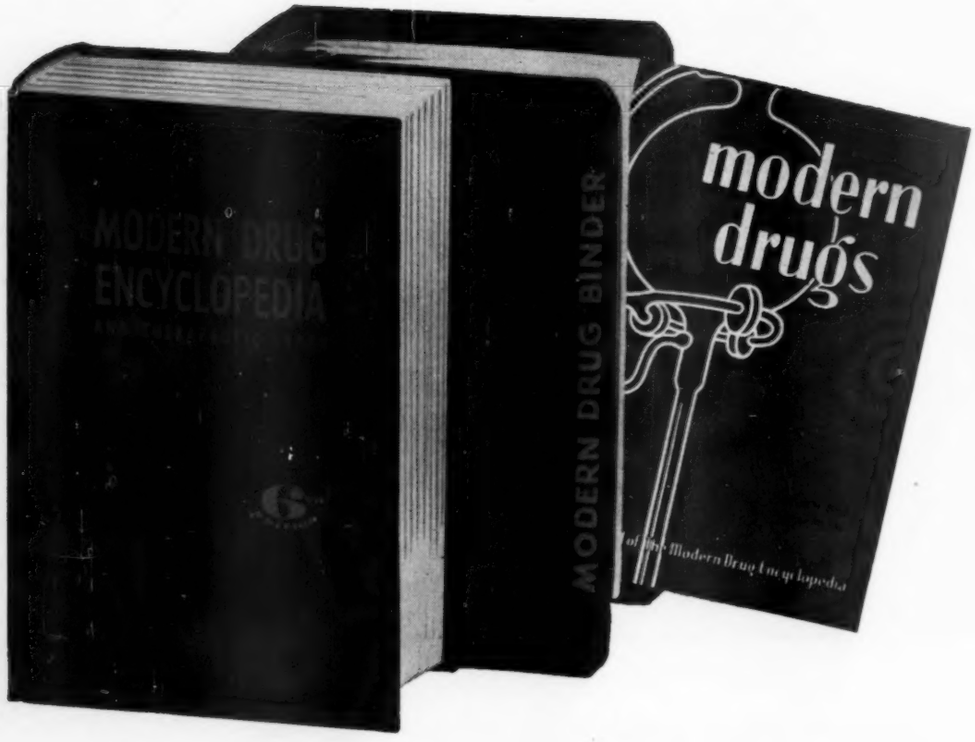

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1. Kramer, P.: Med. Clin. North America, 39:1381, Sept. 1955.
2. Morrison, Samuel: Am. J. Gastroenterology 22:309 (1954).
3. Rossett, N. E., Rice, M. L., Jr., Gastroenterology 26:490 (1954).

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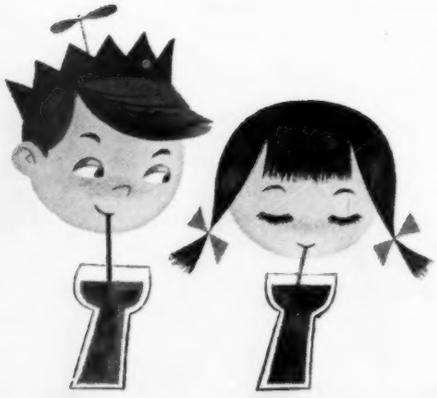

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